Review paper

Gastrointestinal symptoms in COVID-19

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Abstract

SARS-CoV-2 infection manifests mainly by involving the respiratory system. Due to the presence of abdominal symptoms, the digestive system is clearly involved in the expression, transmission, and possible pathogenesis of COVID-19. There are many theories regarding the development of abdominal symptoms, including angiotensin 2 receptor, cytokine storm, and disturbances of the intestinal microbiome. This paper provides an overview of the most important meta-analyses and publications on gastrointestinal symptoms and the gut microbiome in COVID-19.

Introduction

The 2019 coronavirus disease (COVID-19) can be clinically characterized as a pneumonia that often leads to respiratory failure; the gastrointestinal (GI) tract is strongly involved, which translates into the disease's manifestation and possible transmission. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters a host cell through a receptor on its surface. This receptor is the angiotensin-converting enzyme 2 receptor, which is more numerous in the GI tract than in the respiratory system [1–3]. The genetic material of the virus has been detected in stool in up to 50% of patients. It is possible that an intestinal infection may adversely affect lung infection through changes in the intestinal microbiome, the phenomenon of cytokine storm, and increased intestinal permeability [1, 4–8]. Abdominal symptoms are common among COVID-19 patients, but reports regarding their frequency or impact on disease course are contradictory.

Studies published at the beginning of the pandemic suggested that GI symptoms occur in less than 10% of patients; this was confirmed in the last 2 meta-analyses [9–13]. However, the results of most studies suggest that abdominal symptoms are more common – from 30% to 60% [14–17]. The issue of abnormal laboratory test results concerning liver function has also been raised, estimated to occur in 15% to 50% of cases [9, 12, 13, 15]. The effect of GI involvement on the severity of COVID-19 is still unclear [18–21].

Gastrointestinal symptoms

Cheung *et al.*, in their study and meta-analysis of findings from publications, found that 17.6% of patients with COVID-19 had GI symptoms. Moreover, virus RNA was detected in the stool samples of 48.1% of patients. Among 25.4% of patients who presented GI symptoms, the most common symptom was diarrhoea in 22%, followed by abdominal pain/discomfort in 11.9%, and vomiting in 1.7% of patients. Stool viral RNA was found in 15.3% of cases, and it was higher among those with diarrhoea. For the meta-analysis of all GI symptoms, Cheung et al. took into consideration 4243 patients with COVID-19 from 60 studies. The most common symptom, described by 26.8% of the cohort, was lack of appetite, which is not very specific. Diarrhoea was the second most common, in 12.5% of patients, followed by nausea/vomiting in 10.2%, and abdominal pain/discomfort in 9.2%. Significant hetero-

geneity was seen for anorexia, nausea/vomiting, and diarrhoea. Chueng *et al.* concluded that the actual prevalence of any GI symptoms could be underestimated because many earlier studies did not report symptoms other than diarrhoea, and they also pointed to the probability of faecal transmission. They also showed many similarities to SARS and MERS infections [22].

In a multicentre cohort study across 9 hospitals in the United States, a total of 318 patients with confirmed COVID-19 were included. Overall, 61.3% of the patients reported at least 1 GI symptom on presentation; the most common were loss of appetite (34.8%), diarrhoea (33.7%), and nausea (26.4%) [16]. The frequency of GI symptoms in this study was higher than in studies from China.

In the largest meta-analysis, which was performed by Tariq *et al.*, a total of 78 studies with 12,797 patients were included. Among the GI symptoms, loss of appetite occurred in 22.3% of the individuals, diarrhoea in 12.4%, nausea/vomiting in 9.0%, and abdominal pain in 6.2%. Mortality in the group of GI symptoms was 0.4%, which was similar to the overall mortality (2.1%; $p = 0.15$). Significant heterogeneity was reportedin the diarrhoea and nausea/vomiting. They summarized that GI symptoms are seen up in up to 1 in 5 patients with COVID-19. The highest prevalence was for anorexia, whereas the other symptoms occurred in up to 10% of patients. Tariq *et al.* concluded that this must be understood with caution because variable follow-up, lack of uniform criteria for mortality, and lack of adjustment for confounders would prevent proper estimation of mortality. The amount of diarrhoea and nausea/vomiting were lower in the studies from China than in studies conducted outside China, probably due to increasing knowledge and awareness of the presence of GI symptoms. They pointed out that patients with mild disease were not admitted to the hospital, which could affect estimates of symptom prevalence. Also, the exclusion of this group means that GI symptoms may beunderreported. Moreover, in the included studies there was no information on GI-specificlaboratory tests, endoscopy reports, histopathology reports, or imaging. The overall mortality was similar to the mortality in patients with GI symptoms, so there was no uniform definition for COVID-19-attributable mortality [23]. Standardization is crucial, so the following should be defined: death due to the infection itself or to comorbid disease, and the time frame. The systemic review did not assess the effect of different factors, such as age or comorbid diseases.

Elmunzer *et al.* examined the occurrence and influence of abdominal symptoms on the course of COVID-19. 1992 patients from 36 centres were included in the study. A regression analysis was performed to assess the association between digestive symptoms and the severity of COVID-19. Of the 1992 patients, 53% experienced at least 1 GI symptom at any time during the disease, the most common ones being diarrhoea (34%), nausea (27%), vomiting (16%), and abdominal pain (11%). In 74% of the cases, the GI symptoms were mild. After adjusting for potential confounders, the presence of GI symptoms at any time (odds ratio (OR) = 0.93; 95% CI: 0.76–1.15) or liver test abnormalities on admission (OR = 1.31; 95% CI: 0.80–2.12) were not associated independently with mechanical ventilation or death. In their conclusions, they emphasized that GI symptoms and liver function test abnormalities were common, but most were mild and not associated with a more severe clinical course [24].

The concept of the gut-lung axis in COVID-19

In the human gut, the existing microbiome consists of 10^{14} microorganisms, including bacteria, archaea, viruses, and fungi [25]. Bacteria of the genera *Actinobacteria, Firmicutes, Proteobacteria,* and *Bacteroidetes* should dominate the composition of the normal intestinal microbiome [26]. It positively influences various physiological functions in the human body and exerts a key role through its protective, trophic, immunomodulatory, and metabolic effects. The presence of beneficial microorganisms in the respiratory tract, mainly in the lungs, has also been described [27]. *Bacteroidetes* and *Firmicutes* are considered to be the dominant bacteria in the intestine. A similar relationship has been proven in the respiratory tract where *Bacteroidetes, Firmicutes,* and *Proteobacteria* are present [28]. The relationship between the presence of similar strains of bacteria in the intestine and the lungs is associated with the exchange between the intestinal microbiota and the lungs and is defined as the "gut-lung axis" [29]. The fact that endotoxins and metabolites produced by bacteria (e.g. during pneumonia) in the bloodstream can induce changes in the intestinal microbiome suggests that this axis is bidirectional [30]. A deterioration in the composition of the intestinal microbiome has been demonstrated in respiratory infections [31]. The theory that improving the composition of the gut microbiome may benefit and reduce inflammation in the lungs seems to be valid. Current data show that disturbance of the gut microbiome during infection with SARS-CoV-2. COVID-19 is most often pneumonia, which can sometimes lead to acute respiratory distress syndrome (ARDS) [32]. There are reportsof a role of the gut microbiome in the pathogenesis of sepsis and ARDS [33]. Additionally, it is well known that deterioration of the quality of the

intestinal microbiome, i.e. dysbiosis, may thenbe associated with many diseases or may worsen the course of comorbidities [34].

Gut microbiota in COVID-19

Zuo *et al.* investigated changes in the intestinal microbiome of patients with confirmed SARS-CoV-2 infection during hospitalization and assessed the relationship between the disease severity and the excretion of viral genetic material in the faeces. They performed shotgun metagenomic sequencing on faecal samples from 15 COVID-19 patients. During hospitalization, samples were taken 2 or 3 times a week. Patients with SARS-CoV-2 infection had significant changes in their gut microbiome compared with the controls, characterized by an enrichment of opportunistic pathogens and a depletion of beneficial commensals during hospitalization and at all time-points during hospitalization. Depleted symbiotes and gut dysbiosis persisted even after SARS-CoV-2 infection. An abundance of *Coprobacillus* spp., *Clostridium ramosum,* and *Clostridium hathewayi* at baseline correlated with the severity of COVID-19; there is an inverse correlation between the abundance of *Faecalibacterium prausnitzii* (an anti-inflammatory bacterium) and theseverity of the disease. During hospitalization, *Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis*, and *Bacteroides ovatus* – which downregulate angiotensin-2-converting enzyme expression in the gut of mice – inversely correlated with SARS-CoV-2 burden in patients' stool samples. They found permanent changes in the fecal microbiome during hospitalization compared with the control group. The changes in the microbiota were associated with the levels of SARS-CoV-2 and COVID-19 in the faeces. Moreover, the reduction of ACE2 expression in the intestines of mice showed a significant inverse correlation with the viral load of SARS-CoV-2 in the faeces of COVID-19 patients [35].

Probiotics in COVID-19

The response to SARS-CoV-2 infection may be regulated by the gut microbiome, which is instrumental in maintaining optimal immune function by preventing an excessive inflammatory response. Microorganisms serve as a source of microorganism-associated molecular patterns (MAMPs) as well as pathogen-associated molecular patterns (PAMPs). Both are recognizable on host cells by pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs) and nucleotide binding receptors [36]. TLRs recognize MAMPS and PAMPs among other molecules and elicit different immune responses depending on the cell type: ligand or receptor. PRR training with expression of innate cells with microbial/non-microbial ligands of the intestine is needed as a protective mechanism that is independent of adaptive immunity during secondary infection or pathogen exposure [36]. The metabolites secreted by the gut microbiota and immunomodulatory signals, which include short chain fatty acids – such as butyrate, acetate, and propionate – and secondary bile acids secreted by commensals such as *Bifidobacteria* spp., bind to their receptors in cells and macrophages, thereby modulating their metabolism and functions [37]. The introduction of probiotic strains such as *Bifidobacterium lactis* into healthy elderly volunteers resulted in a significant increase in the percentage of mononuclear leukocytes and the anti-tumour activity of NK cells [38]. The composition of a balanced gut microbiota has a great influence on the effectiveness of lung immunity [27]. Disturbances in the gut microbiome due to the widespread use of antibiotics may alsohave a similar effect as that observed in population studies where the increased use of penicillins, cephalosporins, macrolides, and quinolones correlated with an increased risk of lung cancer in humans [39]. Probiotics have shown good results in improving inflammation as well as regulating innate immunity via TLRs and the relevant signalling pathways [40]. Studies based on a mouse model have shown that Treg cells, which downregulate allergic response, can beinduced by the administration of probiotic bacteria such as *Lactobacillus rhamnosus, Bifidobacterium lactis,* and *Bifidobacterium breve* [41]. One conclusion suggests that modulation of the gut microbiota may affect immunity during SARS-CoV-2 infection.

ACE-2 receptor in COVID-19

The ACE2 receptor, through which the virus enters a cell, has many functions in the GI tract, regulating intestinal amino acid homeostasis, modulating the intestinal microbiome, and influencing the expression of antimicrobial peptides, among other things [42]. It has been found that COVID-19 running may reduce the amount of ACE2 in various tissues, which, as with functional diseases, may cause irritable bowel syndrome, disorders of the gut microbiome, and micro-inflammation in the digestive tract, for example [43]. This theory largely explains the occurrence of ailments such as abdominal pain and diarrhoea. In addition, blocking ACE2 appears to be a potential treatment option for SARS-CoV-2, and research is currently underway. Among the new compounds under development is human recombinant soluble ACE-2 (hrs-ACE-2 [APN01; Apeiron Biologics, Vienna, Austria]), which has 2 mechanisms of action that should theoretically be beneficial for COVID-19. The first is to bind the viral peak protein and thus neutralize SARS-CoV-2, and the second is to minimize dam-

age to many organs, including the lungs, kidneys, and heart, due to the unrelenting hyperactivation of the renin-angiotensin system and increased angiotensin II levels. ACE-2 administration for 4–6 h was tested in 89 patients, namely, healthy volunteers in phase I studies and patients with ARDS in phase II clinical studies, with an acceptable safety profile. Moreover, hrs-ACE-2 can reduce the SARS-CoV-2 load 1000 to 5000 times in *in vitro* cell culture and modified organoid experiments, which directly shows that ACE2 can effectively neutralize SARS-CoV-2 [44].

Cytokine storm in COVID-19

The term cytokine release syndrome (CRS), more commonly known as cytokine storm, is used to describe the abnormal secretion of mediators and associated immunopathological events that occur after severe bacterial and viral infections. CRS is associated with an excessive pro-inflammatory response and an ineffective anti-inflammatory control mechanism, leading to tissue damage. The human immune system plays a pivotal role in eliminating infectious agents such as influenza and coronaviruses by recruiting leukocytes and releasing cytokines. The limited and well-harmonized stimulation of immune responses is usually the body's first mechanism of action to build up defence against any viral infection. Nevertheless, an unregulated and over-exaggerated immune response can alter immune function, leading to tissue damage and organ failure. Gu *et al.* postulated that the production of various cytokines that cause cytokine storms in SARS-CoV-2 patients causes immunopathogenic injuries [45]. Therefore, effectively lowering the levels of pro-inflammatory cytokines in patients with severe COVID-19 is crucial in order to prevent the deterioration of their health. Hojyo *et al.* confirmed that during SARS-CoV-2 infection, the alveolar epithelial cells, macrophages, and circulating monocytes are activated by TLRs, which are among the larger set of PRRs. Thanks to their immune memory, they recognize the threat and then produce a large number of inflammatory cytokines and chemokines that attract even more immune cells, especially monocytes and T cells, causing widespread pneumonia [46]. Xu *et al.* presented the results of autopsies in COVID-19 patients, in which lung-dominated interstitial mononuclear inflammatory infiltrates and severe lymphopaenia with hyperactivated T cells in the peripheral blood were found [47]. Moreover, Qin *et al.* demonstrated that COVID-19 patients also had a lower level of regulatory T lymphocytes, which were more clearly lowered in cases of severe infections [48]. Huang *et al.* proved that patients hospitalized due to a severe course of COVID-19 showed high levels of IL-2, IL-7, IL-10, IL-18, G-CSF, TNF, CXCL10, MCP1, and MIP1α in the serum, which confirms that COVID-19 may be associated with cytokine storming [10].

These findings have led to the hypothesis that the main cause of death in COVID-19 is ARDS due to the cytokine storm. Intravascular coagulation was one of the causes of multi-organ damage mediated mainly by inflammatory cytokines, in particular IL-6 [10, 47, 48]. Patients presented multi-organ failure with coagulation disorders represented by lower platelet counts and increased levels of D-dimers, which were associated with poor prognosis and could explain the presence of microclots in the lungs, limbs, brain, heart, GI organs, and kidneys. Park *et al.* recognized cell apoptosis induced by SARS-CoV-2 infection as another cause of multi-organ failure, leading to vascular leakage and inducing a cytopathic effect on cells [49]. It therefore appears that disease worsening or mortality may also be due to a cytokine storm, including ARDS, from viral lung infection, which is responsible for whole-body multi-organ failure. These inflammatory mediators can also lead to vascular hyperpermeability and may stimulate ACE2-expressing endothelial cells in arteries and veins, which together with viral particles cause systemic inflammation.

Conclusions

We need to understand every possible pathomechanism in the course of COVID-19 as soon as possible. The presence of SARS-CoV-2 RNA in the stool in some patients, as well as GI symptoms and disturbances in the intestinal microbiome, may play an important role in determining the course of this disease. Medicines used to treat COVID-19 can also be considered a cause of GI symptoms, because azithromycin, lopinavir, and ritonavir often cause side effects of diarrhoea, abdominal pain, or nausea [50]. Elderly people, immunocompromised patients, and patients with other comorbidities such as type 2 diabetes mellitus or cardiovascular disorders have a much more severe disease course and a significantly higher risk of death.

Studies published at the beginning of the pandemic suggested that GI symptoms occur in less than 10% of patients [9–13]. However, the results of most studies suggest that abdominal symptoms are more common, from 30% to 60% [14–17]. The issue of abnormal liver function laboratory test results has also been raised, which is estimated to occur in 15% to 50% of cases [9, 12, 13, 15]. The effect of GI involvement on the severity of COVID-19 is still unclear [18–21]. Most studies to date have reported that the presence of abdominal symptoms worsens the course of COVID-19. The reports by Livanos *et al.* and the extensive work carried out in North American centres by Elmunzer *et al.* seem to be an exception. Livanos *et al.* postulated a theory based

on the protective role of GI symptoms on the course of COVID-19. The presence of these symptoms attenuates SARS-CoV-2 and leads to a lower inflammatory response, which in turn reduces the clinical course of the disease [51]. Elmunzer *et al.* concluded that GI symptoms and liver test abnormalities were common in patients hospitalized with COVID-19, but that the majority were mild and not associated with a more severe clinical course [25]. The current research, however, requires validation; meta-analyses are necessary to clearly establish how abdominal symptoms affect the prognosis of COVID-19 patients.

It is worth noting that in patients with COVID-19, there are numerous data on disturbances in the gut microbiome, so there is a possibility that intestinal dysbiosis may also influence the clinical symptoms of COVID-19. Many probiotics have been shown to improve or relieve lung disease by modulating the immune system. The best way to modulate it is by following a balanced diet, which should be refined depending on the patient's needs. This may improve and accelerate the recovery of patients, especially elderly or immunocompromised people infected with SARS-CoV-2. An effective nutritional strategy and specific functional food targeting the gut microbiome for a specific population group can significantly improve the prognosis of COVID-19 patients. It certainly requires more careful research that can help us in the unequal fight against SARS-CoV-2.

Conflict of interest

The authors declare no conflict of interest.

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