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COVID-19 disease-induced gastrointestinal autonomic dysfunction: Systematic review

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Abstract

BACKGROUND

It is common for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to occur in the gastrointestinal tract, which can present itself as an initial symptom. The severity of coronavirus disease 2019 (COVID-19) is often reflected in the prevalence of gastrointestinal symptoms. COVID-19 can damage the nerve supply to the digestive system, leading to gastrointestinal autonomic dysfunction. There is still much to learn about how COVID-19 affects the autonomic nervous system and the gastrointestinal tract.

AIM

To thoroughly explore the epidemiology and clinical aspects of COVID-19-induced gastrointestinal autonomic dysfunction, including its manifestations, potential mechanisms, diagnosis, differential diagnosis, impact on quality of life, prognosis, and management and prevention strategies.

METHODS

We conducted a thorough systematic search across various databases and performed an extensive literature review. Our review encompassed 113 studies published in English from January 2000 to April 18, 2023.

RESULTS

According to most literature, gastrointestinal autonomic dysfunction can seriously affect a patient's quality of life and ultimate prognosis. Numerous factors can influence gastrointestinal autonomic nervous functions. Studies have shown that SARS-CoV-2 has a well-documented affinity for both neural and gastrointestinal tissues, and the virus can produce various gastrointestinal symptoms by reaching neural tissues through different pathways. These symptoms include anorexia, dysgeusia, heartburn, belching, chest pain, regurgitation, vomiting, epigastric burn, diarrhea, abdominal pain, bloating, irregular bowel movements, and constipation. Diarrhea is the most prevalent symptom, followed by anorexia, nausea, vomiting, and abdominal pain. Although COVID-19 vaccination may rarely induce autonomic dysfunction and gastrointestinal symptoms, COVID-19-induced autonomic effects significantly impact the patient's condition, general health, prognosis, and quality of life. Early diagnosis and proper recognition are crucial for improving outcomes. It is important to consider the differential diagnosis, as these symptoms may be induced by diseases other than COVID-19-induced autonomic dysfunction. Treating this dysfunction can be a challenging task.

CONCLUSION

To ensure the best possible outcomes for COVID-19 patients, it is essential to take a multidisciplinary approach involving providing supportive care, treating the underlying infection, managing dysfunction, monitoring for complications, and offering nutritional support. Close monitoring of the patient's condition is crucial, and prompt intervention should be taken if necessary. Furthermore, conducting thorough research

on the gastrointestinal autonomic dysfunction caused by COVID-19 is vital to manage it effectively.

Key Words: COVID-19; SARS-CoV-2; Gastrointestinal autonomic dysfunction; Long COVID; Post-COVID; Autonomic nervous system

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Core Tip: As a systemic disease, coronavirus disease 2019 (COVID-19) can impact various organs in the human body, including the autonomic nervous system and gastrointestinal tract. Our team conducted a systematic review to understand better the clinical range of COVID-19's impact on gastrointestinal autonomic dysfunction. We examined clinical manifestations, potential mechanisms, diagnosis, differential diagnosis, effects on quality of life, prognosis, management, and prevention. Most of the literature suggests that gastrointestinal autonomic dysfunction can be severe and negatively impact a patient's quality of life and prognosis. As a result, a multidisciplinary approach is needed to manage this dysfunction. However, further research is necessary to study COVID-19-induced gastrointestinal autonomic dysfunction effectively.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first officially described in Wuhan, China. This virus has quickly spread worldwide and caused a pandemic known as coronavirus disease 2019 (COVID-19). The pandemic has presented humanity with numerous challenges, including the rapid transmission rate of the virus, variations in clinical presentations, fast mutation rates, differing laboratory diagnosis guidelines, and various disease management methods[1]. Although the SARS-Cov-2

virus primarily affects the respiratory system, it can impact any organ or system in the human body[2]. Since its emergence at the end of 2019, COVID-19 has presented in unusual and atypical ways worldwide, with a surge in unfamiliar symptoms and manifestations. This suggests that the pandemic may reshape how diseases present themselves, either by generating new types of illnesses or altering the clinical severity and manifestations of existing ones. These atypical presentations of COVID-19 further complicate the burden imposed by the pandemic, making diagnosis and treatment difficult and increasing the risk of disease transmission[3].

It is common for SARS-CoV-2 to infect the gastrointestinal tract, which can lead to initial symptoms, particularly in children[1]. This virus can cause inflammation and damage to the lining mucosa of the intestine by infecting gastrointestinal tract cells. Studies have found that up to 50% of patients experience gastrointestinal symptoms, such as lack of appetite, nausea, vomiting, abdominal pain, and other enteric symptoms[4,5]. Additionally, the severity of the disease often correlates with the frequency of gastrointestinal symptoms[1]. Current research indicates that the gastrointestinal tract can impact the progression of COVID-19, as demonstrated by gastrointestinal symptoms before respiratory symptoms and the persistence of viral shedding from the gut in severe cases with an aggressive clinical course[6,7].

Autonomic dysfunction is a disruption of the autonomic nervous system that can cause gastrointestinal issues due to damage to the nerve supply in the digestive system. This can be caused by various conditions, including viral infections, impacting appetite, digestion, bowel movements, and sexual function. The dysfunction may occur directly due to the underlying disorder's impact on both the autonomic nerve and the gut or indirectly as a delayed consequence of autonomic dysfunction in the gut[8,9]. COVID-19 is a systemic disease that can affect the autonomic nervous system, which supplies the gut, leading to gastrointestinal symptoms[10]. While there are many hypotheses about the mechanism behind this dysfunction, we still need to understand how COVID-19 alters the autonomic nervous system and gastrointestinal tract during long COVID-19.

This systematic review aims to gather and analyze the current evidence regarding the impact of COVID-19 on the gastrointestinal autonomic system. This newly emerged condition has become a concern during the pandemic, and we will examine its epidemiology, clinical manifestations, potential mechanisms, diagnosis, differential diagnosis, effects on quality of life and prognosis, as well as management and prevention.

MATERIALS AND METHODS

To understand our objective thoroughly, we systematically reviewed relevant literature using the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guidelines. We searched multiple electronic databases, including PubMed, PubMed Central, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Embase, Library and Information Science Abstracts, Google Scholar, Scopus, and the National Library of Medicine catalog up until April 18, 2023. Our search keywords included COVID-19, SARS-CoV-2, Gastrointestinal Autonomic Dysfunction, Long COVID, Post-COVID, and Autonomic Nervous System. We limited our search to studies published in English or with an abstract in English. Our search strategy included both "free-full text terms" and "Medical Subject Headings (MeSH) terms," tailored for each database. We considered studies that discussed patients with COVID-19 and gastrointestinal dysfunction with or without autonomic dysfunction, as well as studies on COVID-19 vaccination and its potential side effects on the autonomic nervous and gastrointestinal systems. We included individuals of all ages, sexes, and ethnicities.

We identified 1453 articles, 137 of which were excluded due to duplication. Upon screening the titles and abstracts, we excluded 971 articles. Out of the remaining 345 full-text articles, only 113 met the eligibility criteria. Our study included 33 full-text research articles, two clinical guidelines and consensus, one meta-analysis, three systematic reviews, 59 reviews, five letters to the editor, and 11 case reports. Figure 1 shows the study flow chart. We also conducted citation searches and reviewed articles

available as abstracts only. However, articles with a commercial background were excluded. We extracted data from the qualified studies using a standard form and assessed bias using the "Cochrane Risk of Bias tool." Publication bias was also evaluated using "funnel plots and Egger's test."

RESULTS

Based on our analysis of the studies provided, we discovered that although gastrointestinal autonomic dysfunction is a rare complication of COVID-19, it can significantly impact the patient's quality of life and prognosis. Table 1 outlines various factors that could affect gastrointestinal autonomic nervous functions. Most studies agree that SARS-CoV-2 has a documented affinity for neural and gastrointestinal tissues and can reach the neural tissues through different pathways, as shown in Figure 1. Patients with COVID-19 may experience different gastrointestinal symptoms, as summarized in Table 2. We have included four studies on the prevalence of gastrointestinal autonomic dysfunction, detailed in Table 3, along with the risks of developing these autonomic manifestations in COVID-19, as shown in Table 4. Table 5 and Figure 3 provide information on the prevalence and underlying mechanisms of common gastrointestinal autonomic dysfunction in patients with COVID-19. It is important to note that vaccination against COVID-19 may induce autonomic dysfunction, including gastrointestinal symptoms, in rare but significant situations, as evidenced by the nine studies outlined in Table 6. COVID-19-induced autonomic effects can significantly impact the patient's condition, general health, prognosis, and quality of life, making early recognition and diagnosis crucial for a positive outcome. Differential diagnosis should also be considered, as detailed in Table 7, as other diseases could induce these manifestations. Treating autonomic dysfunction can be a challenge, as highlighted in Table 8, which provides a simplified description of various treatment modalities.

DISCUSSION

The enteric nervous supply of the gastrointestinal tract

The enteric nervous system is also known as the second brain due to its complex network of neurons lining the gut, with over 100 million neurons and plenty of essential neurotransmitters. It consists of intrinsic enteric neurons, extrinsic sympathetic and parasympathetic projections, and visceral afferent neurons. The intrinsic neurons comprise the outer myenteric and inner submucosal plexuses. The myenteric plexus (Auerbach) is found between the muscle layers of the gastrointestinal tract, while the submucosal plexus (Meissner) lies between the mucosa and the smooth muscle layers. The myenteric plexus is crucial in initiating and controlling smooth muscle motor activities, including peristalsis[11].

The submucosal plexus coordinates gastrointestinal reflexes, such as enzymatic secretion, nutrient absorption, and smooth muscle activities. The intrinsic enteric system operates independently of the autonomic nervous system, providing substantial autonomy over gastrointestinal functions. However, it does receive central input from the parasympathetic and sympathetic nervous systems[11,12]. In addition to neurons, non-neuronal related cells are present, such as enteric glial and Interstitial cells of Cajal. Enteric glial cells create a diffusion barrier surrounding the capillaries around the ganglia, similar to the blood-brain barrier. Interstitial cells of Cajal are electrically coupled to the muscle and act as pacemaker cells, generating spontaneous electrical slow waves and facilitating inputs from motor neurons[13].

The gastrointestinal tract receives its sympathetic neural supply from the abdominal prevertebral ganglia located in the thoracic and lumbar segments of the spinal cord, such as the superior mesenteric, coeliac, and inferior mesenteric ganglia. These ganglia are a bridge between the central and peripheral enteric nervous systems to regulate various intestines functions, including blood flow, motility, secretion, epithelial transport, and endocrine cells. The sympathetic stimulation mainly inhibits gastrointestinal motor activity and secretion. It also has a constant inhibitory effect on mucosal secretion and enhances the contraction of gastrointestinal sphincters and blood vessels *via* neural-mediated vasoconstriction[14,15].

The parasympathetic nervous system plays a vital role in regulating gastrointestinal functions, helping to maintain normal secretion, absorption, and movement in the gastrointestinal tract. It is primarily supplied by the vagus nerve from the medulla oblongata and the sacral spinal nerves from sacral segments 2 to 4. The vagus nerve supplies the upper part of the tract from the esophagus to the small intestine, while the sacral nerves supply the lower part from the colon to the anus. When stimulated, the parasympathetic system causes smooth muscle contraction, promotes peristalsis, stimulates glandular secretion, enhances intestinal secretions, increases blood flow, and relaxes the internal anal sphincter, all essential for proper gastrointestinal function[16,17].

Various factors can affect the autonomic nerve supply of the gastrointestinal tract, such as psychological and emotional stress, diet, medications, toxins, hormones, and aging (Table 1). Anxiety and stress stimulate the sympathetic supply while inhibiting the parasympathetic supply to the gastrointestinal tract. On the other hand, moderate exercise can enhance motility and blood flow in the gastrointestinal tract. Still, prolonged or intense exercise can decrease blood flow to the gastrointestinal tract and shift it to the muscles[18]. Certain foods and drugs can also inhibit or stimulate the parasympathetic nervous system. Hormones like cholecystokinin, gastrin, and secretin can enhance the parasympathetic nervous system and stimulate digestive activity[19]. Toxic heavy metals, such as mercury or lead, and alcohol can damage the autonomic nerves of the gastrointestinal tract. Aging also causes neuronal loss in intestinal myenteric and submucosal plexuses, particularly in cholinergic neurons, and corresponding losses of enteric glia[20]. Chronic diseases like diabetes mellitus negatively impact the gastrointestinal autonomic nervous system. Moreover, many neurological disorders, such as Parkinson's disease and multiple sclerosis, can impair digestion and excretion by affecting the gastrointestinal autonomic nerve system[9]. Finally, various infections can induce autonomic dysfunction of the gastrointestinal tract, such as viral gastroenteritis, bacterial infections like diphtheritic polyneuropathy, tetanus, and botulism, COVID-19, acute tick-borne encephalitis virus infections, Lyme

disease, Chagas disease, human rabies, Guillain-Barre syndrome, and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)[21].

COVID-19 disease and long COVID-19

COVID-19 is a highly infectious disease caused by the SARS-CoV-2 virus that can affect any body part. While most people experience mild to moderate symptoms and recover without complications, some may require hospitalization and even face fatal consequences, with more than 6 million deaths worldwide[22]. Unfortunately, some patients, particularly those with severe COVID-19, may experience prolonged effects after recovering from their initial infection, known as Long COVID or Post-COVID Conditions. This condition is identified by persistent symptoms and other COVID-19-related conditions that continue or develop for more than four weeks after the initial stage of infection. It can be multisystemic and may even worsen over time. Additionally, there is a possibility of severe and life-threatening events that can occur even months or years after the primary infection. Long COVID is not a single condition but a collection of potentially overlapping entities with different biological causes, risk factors, and outcomes. It affects at least 10% of COVID-19 patients and can present with over 200 symptoms, impacting multiple organ systems[23].

Long COVID-19 can cause various symptoms, from mild to severe, affecting different body parts. These symptoms may include fatigue, joint pain, cough, chest pain, shortness of breath, headache, sleep problems, brain fog, dizziness, numbness, smell or taste disorders, depression, anxiety, and different patterns of cognitive problems[24]. The root causes of long COVID-19 are not yet fully understood, but it is believed to be related to the body's immune response against the virus or possible organ damage during the acute phase of the viral illness. It is also possible that some viral particles may remain in the body even after the acute phase ends, triggering ongoing symptoms[25]. Many of the symptoms of long COVID-19 are due to autonomic dysfunction, which can lead to cardiac rhythm disturbances, palpitations, postural

hypotension, tachycardia, dyspnoea, chest pain, and various gastrointestinal and digestive symptoms like nausea, vomiting, and diarrhea[10].

Gastrointestinal and neural tropism of SARS-CoV-2

Research has shown that although SARS-CoV-2 primarily affects the respiratory system, it can also cause dysfunction in multiple organs. Liu and colleagues discovered that the virus could target cells in different organs, including the small intestines, pancreas, liver, and other tissues. They also found a potential link between the virus's ability to infect multiple organs and the distribution of ACE2 receptors in these tissues[26]. ACE2 receptors are most highly expressed in the microvilli of the small intestines, particularly in the brush border of intestinal enterocytes in the ileum[27]. They are also found in the colon, oesophageal epithelium, and gastric and duodenal glandular cells. These findings suggest that the gastrointestinal tract could be a potential transmission route and amplification factory for the virus[28,29]. This high viral tropism to the gastrointestinal tract could explain why gastrointestinal symptoms may appear before respiratory symptoms and why the virus can continue in stool even after the infection has resolved[30].

Studies have shown that SARS-CoV-2 can infect gastrointestinal and neuronal cells within two days of exposure and robustly replicate in human cortical astrocytes, converting them to reactive cells with increased growth factor signaling and activated cellular stress[31]. This can result in damage to and impairments of neurological tissues. The virus can enter the cerebrospinal fluid through the blood-brain barrier and reach the brain *via* the damaged motor or sensory nerve endings[32]. Additionally, it is suggested that the enteric nervous system may serve as a portal of entry for the virus into the central nervous system due to the abundance of ACE-2 receptors and TMPRSS2 expression in enteric nerves and glial cells[34]. With the rich neural network supplying the gastrointestinal tract, the enteric nerves play a significant role in SARS-CoV-2 entry into the central nervous system[35].

SARS-CoV-2 can invade the central nervous system by attacking the nerves that supply the respiratory system, including the olfactory, trigeminal, facial, glossopharyngeal, and vagus nerves[36]. In addition, it can enter the central nervous system through the blood or *via* the vagus nerve from the lungs. In two cases, newborns whose mothers had COVID-19 during the second trimester of pregnancy experienced seizures shortly after birth, indicating that the virus can be transmitted to the brain through the placenta[37]. The virus can replicate inside neural cells, a characteristic known as neurotropism, which is increased by the spike protein produced by furin site insertion, resulting in neuronal infections. COVID-19 can also cause a range of neurological complications during both acute and post-acute stages due to severe respiratory disease, cytokine storms, and immune reactions that lead to hypoxia and impaired brain function[38].

General effects of COVID-19 on gastrointestinal health

Although COVID-19 primarily affects the respiratory system, it also significantly impacts the gastrointestinal tract, particularly children. The exact mechanism behind SARS-CoV-2-induced gastrointestinal symptoms remains unclear, but it is suggested that fecal-oral transmission may play a role due to the presence of SARS-CoV-2 RNA particles in fecal matter[39]. The virus can strongly infect cells in the gastrointestinal tract, particularly in the upper esophagus, absorptive enterocytes, hepatocytes, and cholangiocytes, which have increased expression of ACE2 receptors. These receptors allow the virus to enter host cells and interact with the Spike protein of SARS-CoV-2, leading to an inflammatory response that can cause gut dysbiosis, leaky gut syndrome, and invasion of host cells by the virus. The severity of these changes is directly linked to the expression of ACE2 receptors and can worsen or improve gut dysbiosis and the severity of gastrointestinal leakage[40]. SARS-CoV-2 infection also causes gut mucosal infiltration by plasma cells and lymphocytes, which can lead to interstitial edema and deterioration of the intestinal-blood barrier, allowing the spread of endotoxins, bacteria, viruses, and other microbial metabolites into the systemic circulation. This can further

impair the host's response to SARS-CoV-2 infection and lead to multisystem dysfunction, potentially resulting in septic shock[41].

Shedding the virus in the stool can negatively impact the gut, creating an environment that supports the virus's replication and release. This shedding may be a factor in the poor prognosis associated with the virus. Additionally, respiratory disorders caused by SARS-CoV-2 can harm the respiratory tract microbiota, negatively affecting the gut microbiota and digestive tract due to immune dysregulation[42]. This disruption can lead to a long-term reduction in beneficial bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*, and an increase in harmful bacteria, such as *Clostridium ramosum*, *Clostridium hathewayi*, *Coprobacillus*, *Aspergillus*, and *Candida*. Medical comorbidities and the use of certain medications, such as antibiotics, antifungals, antivirals, and steroids, can worsen this dysbiosis[43]. Maintaining a diverse gut microbiota with a predominance of beneficial bacteria can help combat COVID-19 infection.

Gastrointestinal symptoms can manifest during any stage of COVID-19, either at the beginning or as the disease progresses[44]. Table 2 provides a summary of the gastrointestinal symptoms associated with COVID-19. Diarrhea and dysgeusia are the most prevalent, followed by anorexia, nausea and vomiting, and abdominal pain[45].

In some cases, patients may experience gastrointestinal symptoms before respiratory symptoms, which could indicate the gut's influence on the progression of COVID-19. Fecal viral shedding in severe cases may also suggest the gut's impact on prognosis[7]. Studies show that patients with gastrointestinal symptoms tend to have a longer time between symptom onset and hospital admission than those without[46]. Additionally, severe COVID-19 patients are more likely to have gastrointestinal symptoms, with up to 92% of cases and 80% of those in intensive care experiencing them[47].

The results of endoscopic biopsies have revealed that SARS-CoV-2 can enter gastrointestinal cells directly by binding with ACE2 receptors in various locations of the gastrointestinal tract[48]. Additionally, individuals with severe COVID-19 cases and

multisystem inflammatory syndrome may experience hypercoagulable states due to systemic inflammation, hyperinflammation from cytokine storms, and diffuse endotheliitis. This could result in mesenteric vascular thrombosis and small vessel thrombosis of submucosal arterioles, which could cause bowel necrosis[49,50].

Patients can experience ongoing gastrointestinal symptoms even after recovering from a disease. According to Tian and Rong, a woman suffered from diarrhea for two months and later developed abdominal distension and constipation for about three months after fully recovering from the initial illness[51]. They hypothesized that these symptoms could be attributed to the development of irritable bowel syndrome, which may have occurred due to damage to the enteric nervous system or the central nervous center controlling the vagus nerve in the brainstem. This area regulates various autonomic functions, such as cardiac and respiratory functions, alongside appetite, nausea, and vomiting[52].

Epidemiological characteristics of patients with COVID-19 disease-induced gastrointestinal autonomic dysfunction

Although the pandemic has been relatively short-lived, an increasing number of studies show the involvement of the autonomic system in COVID-19. These studies suggest that autonomic dysfunction is not uncommon and could be a critical factor in increasing mortality rates related to the virus[53]. In particular, patients with severe COVID-19 have been shown to experience gastrointestinal autonomic dysfunction, which can cause symptoms such as anorexia, nausea, vomiting, abdominal pain, bloating, diarrhea, or constipation. Other autonomic dysfunctions have also been observed, including abnormal heart rate variability and blood pressure regulation. These symptoms are more prevalent in patients with older age, longer illness duration, and more severe or critical disease. Nevertheless, further research is needed to determine these dysfunctions' prevalence and clinical significance in COVID-19 patients, especially those affecting the gastrointestinal tract[54-56].

Table 3 displays some studies that examine how frequently COVID-19 patients experience gastrointestinal symptoms. One such study by Erdal *et al*[57] found that 21.8% of their 112 COVID-19 patients experienced diarrhea. Another study by Varma-Doyle *et al*[58] noted that five of six patients with dysautonomia experienced gastrointestinal symptoms such as bloating, nausea, vomiting, constipation, irregular bowel movements, and early satiety. Scala *et al*'s research showed that 26.3% of COVID-19 patients developed diarrhea, compared to only 7.9% of the control group[59]. Moreover, Tan *et al*[60] found that patients who did not receive Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) had higher rates of gastrointestinal symptoms compared to those who did, such as diarrhea (14.5% *vs* 6.5%), nausea and vomiting (11.6% *vs* 9.7%), and abdominal pain (6.5% *vs* 2.9%). Finally, a meta-analysis by Mao *et al*[45] found that 15% of COVID-19 patients in 35 studies experienced digestive symptoms, with anorexia, nausea, vomiting, and diarrhea being the most common. Patients who presented with gastrointestinal symptoms may also have a more severe disease course. Further research is needed to understand better the epidemiological characteristics and clinical significance of COVID-19-induced gastrointestinal dysfunction. Table 4 Lists the risk factors that increase the incidence of gastrointestinal autonomic dysfunction.

Pathophysiology of autonomic dysfunction in COVID-19

The exact cause of autonomic dysfunction in COVID-19 and long COVID-19 is still not fully understood. It could be due to the direct effects of the virus on the nervous system, gut dysbiosis, an overactive robust immune response, the impact of hypoxia on neurological tissues, or medication used in the patient's treatment. The virus may invade the autonomic pathway directly or induce injury through the immune response, which can stimulate the sympathetic nervous system and activate pro-inflammatory cytokines, causing further stimulation of the sympathetic system. This can result in the development of a sympathetic storm[10]. Direct SARS-CoV-2 invasion of the medulla or hypothalamus can trigger autonomic dysfunction through retrograde neuronal or

systematic hematogenous routes. At the hypothalamus, targeting GABAergic or glutamatergic interneurons can directly or indirectly impact the paraventricular nucleus (PVN) plasticity, leading to neuroinflammation and autonomic nervous system disruption. Similarly, SARS-CoV-2 invasion of astrocytes and GABAergic interneurons in the nucleus tractus solitaries in the medulla can modulate the normal autonomic function and/or initiate cell death[54].

Studies have shown that COVID-19 patients with excessive sympathetic activation are more likely to experience severe pulmonary capillary leakage, alveolar damage, and an increased risk of developing acute respiratory distress syndrome. This over-activation of sympathetic nervous system is also linked to parasympathetic inhibition and Renin-Angiotensin-System activation[61,62]. On the other hand, stimulating the vagus nerve can have anti-inflammatory effects by inhibiting the release of pro-inflammatory cytokines and modulating sympatho excitation. This could be a therapeutic approach for the autonomic nervous system[63]. Pulmonary chemoreceptors and mechanoreceptors may play a role in spreading SARS-CoV-2 from the lungs to the respiratory center in the medulla oblongata, leading to sudden central respiratory failure[64]. To combat this, beta-receptor antagonists can reduce sympathetic stimulation and limit the interaction between SARS-CoV-2 and ACE2 receptors[65].

Studies have shown that autoimmune antibodies exist in many autonomic nervous system disorders, including postural orthostatic tachycardia syndrome, a subtype of orthostatic intolerance. It is believed that COVID-19 may trigger an autoimmune mechanism that causes dysfunction in the autonomic nerves. According to Al-Beltagi *et al*[66], the effects of SARS-CoV-2 on the immune system are related to the sizeable viral RNA molecules, molecular mimicry, and interaction with the host immune system, as well as the overlap between some viral and human peptides. The virus can also induce tissue damage and create a strong binding between the SARS-CoV-2 S protein and sACE-2. A growing body of evidence suggests that autonomic nervous system dysfunction observed in COVID-19 may be due to an autoimmune response. In a study by Chadda *et al*[67], COVID-19 patients experienced various symptoms of autonomic

nervous system dysfunction, including tachycardia, orthostatic intolerance, and gastrointestinal dysfunction. The researchers suggested these symptoms may be due to an autoimmune response against the autonomic nervous system. Lavi *et al*[68] found that COVID-19 patients had significantly higher levels of autoantibodies against the ANS than healthy controls, which may contribute to the autonomic nervous system dysfunction observed in COVID-19 patients. Additionally, Paterson *et al*[69] found that COVID-19 may trigger autoimmune responses against the nervous system, including the ANS, which may explain the diverse neurological symptoms observed in COVID-19 patients.

Severe COVID-19 often leads to hypoxia, which can cause damage to different parts of the brain, including the dorsal vagal complex located in the medulla oblongata, the lower part of the brainstem. This complex is responsible for various autonomic functions like heart rate, respiration, and food intake. Injuries to the dorsal vagal complex can lead to nausea, vomiting, and other autonomic dysfunction symptoms[70]. Disturbance of the nucleus of tractus solitaries, part of the dorsal vagal complex beside the hypothalamus, causes impaired food intake. Impairment of the gelatinous nucleus, subnucleus part of the nucleus of tractus solitaries, causes respiratory failure in severe cases of COVID-19. It may also be responsible for sudden infant death syndrome due to the alteration of the catecholaminergic neurochemical system[71,72]. COVID-19 can also cause gut dysbiosis, which increases pro-inflammatory cytokines and ultimately leads to neuroinflammation. The cytokines storm associated with severe COVID-19 causes hyperinflammation with increased pro-inflammatory cytokines resulting in gut dysbiosis and compromising intestinal barrier integrity. The increased permeability and leaky gut increase levels of circulating lipopolysaccharides, which ultimately may initiate microglial cell activation and neuroinflammation[73]. Additionally, COVID-19 can induce systemic vascular changes all over the body, including in the gastrointestinal tract, which may result in gastrointestinal autonomic dysfunction[74].

It is imperative to understand that COVID-19 has a severe negative impact on the autonomic nervous system. The downregulation of the IKBKAP gene and the up-

regulation of N-type calcium channels at the molecular level can lead to fatal gastrointestinal dysfunction and complications, including mortality[75,76]. Autonomic dysregulation can manifest in various ways, such as at the level of autonomic centers like the medulla and hypothalamus, in the sympathetic and parasympathetic supply to the gut, or the target organs of the digestive system. The prevalence and mechanism of common gastrointestinal symptoms due to autonomic nervous system dysfunction in COVID-19 patients are detailed in Table 5. Figure 3 comprehensively summarizes the mechanisms that can induce autonomic dysfunction in COVID-19. It is essential to take these findings seriously and take necessary precautions to avoid any complications.

COVID-19 vaccine on gastrointestinal autonomic dysfunction (causation or prevention)

The COVID-19 vaccine has undoubtedly been a great benefit in ending the Corona pandemic. However, some individuals who have taken it have experienced certain effects, such as autonomic dysfunction that affects various body organs and systems, including the gastrointestinal tract. This side effect is uncommon and has been reported infrequently, particularly after receiving certain types of COVID-19 vaccines that rely on DNA and RNA technology, like the Moderna, Pfizer-BioNTech, and Johnson & Johnson vaccines. These vaccines use immunologic liposomes to achieve powerful antigenic stimulation of target cells[77].

Autonomic dysfunction can cause various symptoms, from mild dizziness and light-headedness to more severe symptoms like fainting and arrhythmia. These symptoms may occur shortly after vaccination and last for varying lengths, from a few minutes to many hours[78]. Table 6 provides information on gastrointestinal and autonomic dysfunction related to COVID-19 vaccinations[79-87]. Gastrointestinal complications are typically minor and secondary to primary complications, such as constipation, that may develop as a symptom of rare complications like transverse myelitis or Guillain-Barre syndrome. While serious COVID-19 vaccine-related

complications like acute myocarditis are rare and have unclear pathophysiology, they should be considered if unusual symptoms appear within a few days of vaccination[88].

The exact cause of autonomic dysfunction associated with COVID-19 vaccination is not fully understood. The vaccine's robust immune response may trigger inflammation in the autonomic nervous system, leading to symptoms of autonomic dysfunction[89]. Some patients have experienced reflex syncope or presyncope due to delayed vasovagal reaction, possibly related to stress caused by vaccination[90]. It's important to note that the risk of developing autonomic dysfunction after COVID-19 vaccination is very low. These rare complications should not deter us from reaping the significant protective benefits of these vaccines. The benefits of vaccination in preventing severe COVID-19 disease, hospitalization, and death far outweigh the risks.

Impact of COVID-19-induced gastrointestinal autonomic dysfunction

Gastrointestinal manifestations may occur during the early phase of COVID-119 and could be considered an early indicator of infection, particularly in asymptomatic or mildly symptomatic patients. However, these symptoms are more common in older patients, those with underlying medical conditions, or severe COVID-19. Such patients are at an increased risk of delayed diagnosis, higher levels of inflammatory markers, prolonged illness, severe morbidity, hospitalization, post-COVID-19 complications, and mortality[42,91]. Consequently, gastrointestinal autonomic dysfunction can significantly affect patients' overall health and well-being. Patients with gastrointestinal symptoms may experience a variety of symptoms that can impair their quality of life, such as dysphagia, anorexia, esophageal dysmotility, gastroparesis, bloating, nausea, abdominal pain, small intestinal bacterial overgrowth, diarrhea, or constipation[9]. COVID-19 patients may also experience autonomic nervous system dysregulation, leading to post-infectious irritable bowel syndrome. This condition is characterized by chronic abdominal pain, bloating, and altered or abnormal bowel habits that can persist for at least three months after the initial SARS-CoV-2 infection. It is believed to occur due to persistent neuroinflammation, immune dysregulation, and gut dysbiosis[92].

Additionally, COVID-19 can cause autonomic dysfunction, which may lead to reduced blood flow to the gut and worsen gastrointestinal symptoms. It also increases the risk of thrombotic complications, such as deep vein thrombosis and possibly pulmonary embolism, due to activation of the coagulation cascade and developing endothelial dysfunction[93]. Furthermore, autonomic dysfunction may affect cardiac functions, resulting in changes in heart rate, labile blood pressure, and impaired cardiac output. COVID-19-induced gastrointestinal dysfunction may also be associated with other symptoms of autonomic dysfunction, such as dizziness and fainting[94].

COVID-19 can cause various symptoms that can hinder a patient's recovery. These symptoms may make eating difficult and lead to dehydration, malnutrition, and weight loss, further impacting the patient's health. They can also make a person more susceptible to complications such as gastric ulcers, bleeding, small bowel obstruction, or even perforation[95]. Gastrointestinal symptoms can also significantly impact a patient's mental health, leading to anxiety, depression, and social isolation, which can further worsen their symptoms and impair their ability to function in their daily life[96]. The impact depends on various factors, such as the severity of the illness, the extent of gastrointestinal involvement, general patient condition, and any existing medical conditions. While most cases resolve themselves within a few weeks, some individuals may experience prolonged symptoms[97]. Therefore, it is crucial to identify and treat these symptoms and provide adequate supportive care to enhance patient outcomes. Long-term follow-up is also essential to evaluate potential sequelae in patients with COVID-19-induced gastrointestinal manifestations[98].

Diagnosis of COVID-19-induced gastrointestinal autonomic dysfunction

Diagnosing gastrointestinal autonomic dysfunction in COVID-19 patients depends on their symptoms and clinical examination. However, diagnosing it can be challenging as the symptoms may be similar or overlap with other conditions, and there is no specific test for it. Therefore, a comprehensive evaluation is necessary based on the patient's medical history, symptoms, laboratory tests, imaging studies, and specific tests to assess

autonomic nervous system function. A high level of clinical suspicion is also required[99].

To diagnose COVID-19-induced gastrointestinal autonomic dysfunction, a thorough clinical evaluation is necessary. This includes a detailed medical history and physical examination, emphasizing the duration and onset of autonomic dysfunction symptoms such as nausea, vomiting, abdominal pain, early satiety, diarrhea, weight loss, dizziness, fainting, and blood pressure fluctuations. COVID-19 symptoms like high fever, cough, or shortness of breath should also be evaluated. Medical history should include pre-existing gastrointestinal conditions, systemic premorbid conditions, recent medications, recent travel, and a past or family history of autonomic dysfunction or disorders. Such a history increases the risk of developing COVID-19-induced gastrointestinal autonomic dysfunction[55,100].

During a physical examination, it's important to evaluate vital signs such as blood pressure, heart rate, respiratory rate, hydration status, and sweating. An abdominal examination should also be conducted to check for signs of distension, tenderness, masses, or abnormal bowel sounds[101]. The SCOPA-AUT scale is useful for assessing autonomic function, particularly in individuals with neurological diseases like Parkinson's. This questionnaire assesses multiple aspects of autonomic dysfunction by covering 25 items related to various body regions, including the gastrointestinal tract, urinary system, cardiovascular system, thermoregulatory mechanism, pupillomotor function, and sexual dysfunction (different in males than females). Each item is scored from 0 (never) to 3 (often happening), with higher scores indicating more severe dysfunction[102,103]. Researchers have used this scale to evaluate autonomic dysfunction in patients with COVID-19 and found that many patients might have persistent symptoms of autonomic nervous system dysfunction following the acute phase of COVID-19 that might deteriorate and impair clinical recovery[57].

To determine the underlying cause of a patient's symptoms, laboratory tests can help rule out other diseases. It is important to confirm a diagnosis of COVID-19 to establish the presence of SARS-CoV-2. Blood tests can provide valuable information,

such as a complete blood count, inflammatory markers like CRP, blood glucose levels, comprehensive metabolic panel, serum electrolyte levels, serum amylase and lipase levels, liver function, and kidney function. These tests can help evaluate for anaemia, dehydration, electrolyte imbalances, kidney function, pancreatic function, liver function, and other underlying disorders contributing to the patient's symptoms. Additionally, stool analysis can identify signs of inflammation or infection and detect any pathogens, such as viruses or bacteria, that could be causing gastrointestinal symptoms or any other abnormalities[104,105].

To assess autonomic dysfunction in specific areas of the gastrointestinal tract, specialized tests may be necessary. For instance, COVID-19 can cause gastrointestinal dysfunction, which may manifest as esophageal motility issues. Evaluating esophageal motility can help determine the functionality of the muscles responsible for moving food into the stomach. Delayed gastric emptying is a symptom of gastroparesis, which can be assessed through electrogastrography or gastric emptying studies to determine the speed at which food moves through the stomach[9]. A colonic transit study can also evaluate food movement through the colon in cases of suspected constipation or delayed colonic transit. Anorectal manometry may be used to assess the function of the anal or rectal areas in cases of suspected anorectal dysfunction[106]. Tests can also be conducted to evaluate the autonomic nervous system, such as heart rate variability measurements, blood pressure positional changes, and sweat testing. Electrocardiograms may be utilized to evaluate heart rate and rhythm, as arrhythmia and abnormal heart rate variability are common symptoms of autonomic dysfunction[107]. Sweat testing using quantitative sudomotor axon reflex may also be used to diagnose autonomic dysfunction by evaluating the function of sweat glands, as abnormal sweating is a possible symptom. In addition, the tilt table test can also be utilized to investigate unexplained fainting, which may be associated with gastrointestinal autonomic dysfunction[109]. Endoscopy may be performed to evaluate the structure and function of the gut or to confirm the presence of inflammation, hemorrhage, perforation, damage, or infection in the gastrointestinal tract[110]. Imaging,

such as abdominal X-rays, ultrasonography, computed tomography scans, or magnetic resonance imaging, may also be necessary to evaluate for bowel obstruction, perforation, motility disorders, structural abnormalities, inflammation, or other underlying conditions that may be causing gastrointestinal symptoms[111,112].

Differential diagnosis of COVID-19-induced gastrointestinal autonomic dysfunction

Diagnosing gastrointestinal autonomic dysfunction can be a difficult task, as its symptoms can mimic those of other gastrointestinal disorders. Conducting a thorough differential diagnosis is important to rule out other conditions and confirm the diagnosis of COVID-19-induced gastrointestinal autonomic dysfunction. This can be achieved through detailed physical examinations, stool and blood tests, imaging studies, and other diagnostic methods. Table 7 outlines some conditions that should be considered during the differential diagnosis process.

Treatment

Managing COVID-19-induced gastrointestinal autonomic dysfunction is an evolving and growing field with a multi-faceted approach. The optimal management approach depends on the individual patient's presentation and underlying conditions. The treatment needs a multidisciplinary approach with symptomatic treatment, specific treatment, pharmacological and non-pharmacological interventions, dietary modifications and management, supportive care, management of complications, and follow-up care[55]. The collaboration of a gastroenterologist, neurologist, intensivist, nutritionist, and infectious disease specialist helps to achieve proper management. Other specialties may be needed according to the patient's condition[97]. Early identification and well-timed management of these disorders can improve patient outcomes. In severe conditions, timely management of complications is essential to prevent adverse outcomes. Patients should be instructed to obtain medical attention if symptoms persist or worsen. Follow-up is mandatory, and the resolution of the

infection should be confirmed with repeated testing when necessary[113]. A summary of the proposed treatment is shown in Table 8.

Managing COVID-19-induced gastrointestinal autonomic dysfunction is a constantly evolving field that requires a multifaceted approach. The best approach for managing this condition depends on the individual patient's symptoms and any underlying medical conditions they may have. Treatment involves a multidisciplinary team that provides symptomatic and specific treatment, pharmacological and non-pharmacological interventions, dietary modifications, supportive care, management of complications, and follow-up care[55]. A collaboration between a gastroenterologist, neurologist, intensivist, nutritionist, and infectious disease specialist is necessary to ensure proper management. Depending on the patient's condition, other specialties may also need to be consulted[97]. Early identification and timely management of gastrointestinal autonomic dysfunction can improve patient outcomes. In severe cases, prompt management of complications is crucial to prevent adverse outcomes. Patients should seek medical attention if their symptoms persist or worsen. Follow-up care is essential, and the resolution of the infection should be confirmed with repeated testing when necessary[113]. Please refer to Table 8 for a summary of the proposed treatment.

It is important to note that the study has certain limitations which may impact its findings. Due to the inclusion of a vast number of studies, there is some variation in the articles' designs, quality, population, and outcomes measured. This variation can make drawing comparisons and synthesizing the results difficult. Furthermore, it is worth noting that not all relevant studies were reviewed, particularly those published in languages other than English or those not accessible through major databases.

CONCLUSION

The gastrointestinal tract is a common target of SARS-CoV-2 infection and could induce the initial presenting manifestation. COVID-19-induced gastrointestinal autonomic dysfunction can be a significant complication affecting patients' well-being and prognosis. Due to the unclear mechanism behind these manifestations, further research

is necessary. Additionally, some COVID-19 vaccines may trigger autonomic dysfunction. Several factors can increase the risk of developing gastrointestinal autonomic nervous functions and exacerbate their impact on patients. Diagnosing COVID-19-induced gastrointestinal autonomic dysfunction can be challenging, requiring careful clinical evaluation, specific laboratory tests, and imaging studies. Early detection and management of these disorders can improve patient outcomes and prevent long-term complications.

ARTICLE HIGHLIGHTS

Research perspectives

A multi-faceted approach is essential to ensure the best outcome for those affected by coronavirus disease 2019 (COVID-19). This includes providing supportive care, addressing the root infection, managing dysfunctions, monitoring for complications, and providing nutritional aid. It is crucial to closely monitor the patient's condition and take prompt action if needed. Furthermore, in-depth research on COVID-19-induced gastrointestinal autonomic dysfunction is vital for proper management.

Research conclusions

To achieve optimal results for individuals with COVID-19, it is crucial to adopt a multidisciplinary approach, which includes providing supportive care, treating the underlying infection, managing any dysfunction, monitoring for complications, and offering nutritional assistance. It is imperative to closely monitor the patient's condition and take swift action if necessary. Additionally, conducting comprehensive research on the gastrointestinal autonomic dysfunction caused by COVID-19 is critical for effective management.

Research results

Gastrointestinal autonomic dysfunction is a condition that can greatly impact a patient's quality of life and prognosis, according to most literature. There are many factors that

can affect the functioning of the gastrointestinal autonomic nervous system. Studies have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a documented affinity for both neural and gastrointestinal tissues, which can lead to various gastrointestinal symptoms. These symptoms include anorexia, dysgeusia, heartburn, belching, chest pain, regurgitation, vomiting, epigastric burn, diarrhea, abdominal pain, bloating, irregular bowel movements, and constipation. Diarrhea is the most common symptom, followed by anorexia, nausea, vomiting, and abdominal pain. While COVID-19 vaccination may rarely cause autonomic dysfunction and gastrointestinal symptoms, COVID-19-induced autonomic effects can significantly impact a patient's health, prognosis, and quality of life. Early diagnosis and proper recognition of the condition are crucial for better outcomes. It is important to consider other potential causes of these symptoms, as they may not always be caused by COVID-19-induced autonomic dysfunction. Treating this condition can be a challenging task.

Research methods

We conducted a comprehensive and systematic exploration of multiple databases, followed by an extensive analysis of relevant literature. Our review included 113 studies published in English between January 2000 and April 18, 2023

Research objectives

Our objective is to thoroughly investigate the epidemiology, clinical manifestations, potential mechanisms, diagnosis, differential diagnosis, and impact of gastrointestinal autonomic dysfunctions on the quality of life and prognosis of individuals who have contracted SARS-CoV-2. Additionally, we will explore management and prevention strategies.

Research motivation

Due to the importance of gastrointestinal tract autonomic dysfunction in patients with COVID-19, we are motivated to conduct this systematic review concerning this newly emerged condition that has become a concern during the pandemic.

Research background

It is typical for SARS-CoV-2 infection to affect the gastrointestinal tract, which may manifest as an early warning sign. The frequency of gastrointestinal symptoms often indicates the seriousness of COVID-19. COVID-19 may impair the nerve supply to the digestive system, resulting in autonomic dysfunction of the gastrointestinal tract. There is still much to discover about the impact of COVID-19 on the autonomic nervous system and the gastrointestinal tract.

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