Received: 16 June 2022 | Accepted: 10 August 2022

DOI: 10.1002/jmv.28067

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

COVID-19 and inflammatory bowel disease crosstalk: From emerging association to clinical proposal

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Funding information

National Natural Science Foundation of China; Anhui Provincial University Natural Science Research Project; Anhui Provincial Natural Science Foundation

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause coronavirus disease 2019 (COVID-19), an acute respiratory inflammation that has emerged worldwide since December 2019, and it quickly became a global epidemic. Inflammatory bowel disease (IBD) is a group of chronic nonspecific intestinal inflammatory diseases whose etiology has not been elucidated. The two have many overlapping symptoms in clinical presentation, such as abdominal pain, diarrhea, pneumonia, etc. Imbalance of the autoimmune system in IBD patients and long-term use of immunosuppressive drugs may increase the risk of infection; and systemic symptoms caused by COVID-19 may also induce or exacerbate intestinal inflammation. It has been found that the SARS-CoV-2 receptor angiotensin converting enzyme 2, which is highly expressed in the lung and intestine, is an inflammatory protective factor, and is downregulated and upregulated in COVID-19 and IBD, respectively, suggesting that there may be a coregulatory pathway. In addition, the immune activation pattern of COVID-19 and the cytokine storm in the inflammatory response have similar roles in IBD, indicating that the two diseases may influence each other. Therefore, this review aimed to address the following research questions: whether SARS-CoV-2 infection leads to the progression of IBD; whether IBD increases the risk of COVID-19 infection and poor prognosis; possible common mechanisms and genetic cross-linking between the two diseases; new treatment and care strategies for IBD patients, and the feasibility and risk of vaccination in the context of the COVID-19 epidemic.

KEYWORDS

ACE2, COVID-19, IL-17, inflammatory bowel disease, SARS-CoV-2

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1 | INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) has swept the world in a short time and quickly become a pandemic threatening world public health. COVID-19 infection can lead to increased secretion of proinflammatory factors, such as tumor necrosis factor (TNF)-α and interleukin (IL)-17, and can significantly increase the circulating level of various inflammatory factors. Macrophages and neutrophils that accumulate in the blood are further activated and spread throughout the body with the blood. Some virus-susceptible organs are flooded with cytokines and release bioactive substances, which will trigger cytokine storms and cause great damage locally. The clinical manifestations of COVID-19 patients are diverse. While the common symptoms of the COVID-19 are in the respiratory tract, some patients also have nausea, vomiting, abdominal pain, diarrhea and other gastrointestinal (GI) complications.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA can be detected in the stool examination of a large number of patients, suggesting that COVID-19 may also invade the GI tract, which is the largest immune interface between the human body and the environment, constantly exposed to various antigens and potential immune stimuli.[2] Moreover, it has been found that in addition to complications during illness, COVID-19 patients are often observed to experience late-onset complications, including interstitial pneumonia, cytopenia, arthralgia, myocarditis, and autoimmune diseases.[3–9] Emerging reports suggest that COVID-19 may lead to autoimmune and autoinflammatory diseases, which in turn lead COVID-19 patients to enter a vicious circle of infection and are closely associated with increased morbidity and mortality.[4,8,10] Among these studies, great attention has been focused on inflammatory bowel disease (IBD) which have a lot of overlap with COVID-19 in clinical symptoms and immune activation patterns.[11–16]

IBD is a group of diseases, with an abnormal immune system and mainly characterized by nonspecific intestinal inflammation. Ulcerative colitis (UC) and Crohn's disease (CD) are common IBD. IBD is more common in adolescents, and its prevalence in males and females is similar.[17] It is characterized by alternating periods of activity and remission, and is difficult to cure. It is mainly manifested as recurrent abdominal pain, diarrhea, bloody stools, and sometimes extraintestinal symptoms may also invade the lungs. The activation of Th1, and Th2 and Th17 inflammatory pathways caused by various factors, increase the secretion of inflammatory cytokines, and imbalance of protective factors/risk factors, such as intestinal angiotensin converting enzyme (ACE)-2/ACE, can lead to persistent inflammation of the intestinal mucosa and immune disorders of the digestive system in patients with IBD. The ACE2 receptor, the “guide” for SARS-CoV-2 to invade the organism, is upregulated in IBD patients. However, whether the repeated disruption of the gut in IBD contributes to susceptibility to COVID-19 or a change in the course of preexisting COVID-19 is unknown.

Due to the similar immune activation patterns and inflammatory response pathways between COVID-19 and IBD, the clinical symptoms of the two also have a lot of overlap. As an immune disease, immunomodulators and biologics are very beneficial to the remission and regulation of IBD. However, whether these drugs have an impact on the occurrence and prognosis of COVID-19 has not yet been elucidated. Based on the available evidence, it can be speculated that there is an association between COVID-19 and IBD. In the present review, we summarized the possible relationship and shared etiology between COVID-19 and IBD. On this basis, the proper drug treatment and care, as well as the feasibility and risk of vaccination for IBD patients during the COVID-19 pandemic were explored.

2 | OVERVIEW OF COVID-19 AND IBD

2.1 | Overview of COVID-19

COVID-19, caused by SARS-CoV-2, is a highly contagious viral pneumonia that affects multiple organ systems.[18,19] SARS-CoV-2 is the seventh human coronavirus found so far, it is a single strand positive strand RNA virus with an envelope, and its RNA genome is about 30 KB. SARS-CoV-2 is mainly transmitted through respiratory droplets and close contact.[20] SARS-CoV-2 binds to human ACE2 on the cell membrane through the S1 subunit of the receptor binding domain (RBD). The affinity between SARS-CoV-2 RBD and ACE2 is several times that of SARS-CoV RBD, which may be the reason why SARS-CoV-2 has stronger infectivity and a wider epidemic range.[21,22]

At present, COVID-19 still poses a huge threat to human society, seriously affecting the economy, politics, transportation, and people's lives of all countries.[23] COVID-19 usually presents with fever, dry cough and fatigue, sometimes involving the digestive system, abdominal pain, diarrhea, and other symptoms. Severely infected patients can rapidly develop acute respiratory distress syndrome, metabolic acidosis, disseminated intravascular coagulation (DIC), septic shock, and multiple organ failure, etc.[24] In COVID-19, the virus invades the lower respiratory tract and infects type II alveolar cells, resulting in apoptosis and loss of pulmonary surfactant. A large number of cytokines rapidly appeared in the local immune microenvironment, producing a “tornado”-like destructive force, eventually lead to capillary leakage and aggravate pulmonary edema.[25] At present, there is no specific medicine for the treatment of COVID-19. For infected persons, the respiratory tract should be kept open, and tracheal intubation and mechanical ventilation should be given as adjuvant treatment to prevent acute respiratory failure, which are combined with antivirals (eg, remdesivir, favipiravir), targeted immunomodulatory therapies (eg, tocilizumab, sarilumab, anakinra, ruxolitinib), intravenous immunoglobulin, anticoagulation, etc.[26]

2.2 | Overview of IBD

IBD is a disease with an abnormal immune system caused by the joint action of genetic factors and environmental factors. It mainly includes UC and CD.[27] In recent years, the incidence and prevalence of IBD

have been on the rise worldwide.[28,29] Since this disease cannot be cured and most patients are diagnosed early in life, the cost of continuous treatment and medical treatment is very high, which brings a huge burden to the family and society.[30] The pathogenesis of IBD can be simply summarized as follows: environmental factors act on genetically susceptible individuals, and with the participation of gut microbes, cause intestinal immune imbalance, damage the intestinal mucosal barrier, and lead to persistent inflammatory damage to the intestinal mucosa.[27,31] It was found that Th17 cells and IL-23/IL-17 axis are closely related to the pathogenesis of immune-mediated inflammatory diseases. Numerous clinical trials have revealed the therapeutic effects of cytokine inhibitors in IBD by modulating IL-17 and related pathways.[32]

For IBD, treatment is mainly to relieve symptoms and improve the patient's life. Aminosalicylic acid preparations (5-aminosalicylic acid [5-ASA], sulfasalazine [SASP]), glucocorticoids (prednisone, hydrocortisone, methylprednisolone), immunomodulators (azathioprine, thiopurine, thioguanine, methotrexate, tacrolimus, mycophenolate mofetil), biological agents, etc. are commonly used in the clinic. At the same time strengthen nutrition, if necessary, surgical treatment to remove the diseased intestinal segment.[33]

3 | ASSOCIATION BETWEEN COVID-19 AND IBD

COVID-19 patients have been proposed to be more likely to experience clinical autoimmunity, due to the immune tolerance and autoimmune responses induced by SARS-CoV-2.[34] Although the clinical manifestation of COVID-19 is mainly the destruction of the respiratory system, numerous studies from different countries have revealed various GI symptoms in COVID-19 patients, especially nausea, abdominal pain, and diarrhea.[35] It was reported that the first infected person in the United States had a history of nausea and vomiting for 2 days before admission, and then had loose stool and abdominal discomfort after hospitalization.[36] Among 651 Chinese patients diagnosed with COVID-19 in early 2020, 74 patients developed at least one kind of GI symptoms (nausea, vomiting, and diarrhea), accounting for 11.4% of the total subjects, of which diarrhea was the most common GI abnormality.[37] Viral RNA can be detected in fecal samples of 48.1% of COVID-19 patients, even after respiratory tract samples are negative. The above evidence suggested that the impact of SARS-CoV-2 on the GI tract may be more likely, lasting longer and hidden than we thought.[38] Therefore, it is reasonable to speculate that COVID-19 may be associated with IBD, an immune disease of the digestive system.

At present, whether COVID-19 plays a role in the progression of IBD and what roles it plays; whether IBD will interfere with the pathogenesis and prognosis of COVID-19 has not been clearly elucidated. Viganò et al.[39] investigated 709 patients with IBD, of which 53 were simultaneously infected with COVID-19. Their study found that diarrhea accounted for 49% of patients with both IBD and COVID-19, which were significantly higher than that of people with only IBD. At the same time, severe active IBD was significantly associated with COVID-19. Similar results were observed in the study of Derikx et al[11] that about 38.6% for IBD patients infected with COVID-19 had diarrhea symptoms. The probability of digestive system disorder of COVID-19 in IBD patients is higher than that of people infected only with COVID-19 or IBD, suggesting that COVID-19 may be related to aggravate the symptoms of IBD or promoting its conversion to the active phase. A large nationwide cohort study in the Netherlands compared the incidence of COVID-19 in patients with IBD and the general population. Interestingly, there were no significant differences in COVID-19 morbidity and mortality in the IBD group compared with the control group, but the hospitalization rate was lower.[11] Similar results were found by Singh et al.[40] As of now, there are few references available, and it is too early to infer a direct causal relationship between COVID-19 infection and IBD activity. Considering the information currently reported, it can be hypothesized that COVID-19 may advance the active phase in the development of IBD or worsen the complications of IBD.

3.1 | Can SARS-CoV-2 infection trigger IBD development?

It has been found that the incidence rate of IBD increased during the outbreak of COVID-19.[41] SARS-CoV-2 can enter human cells through the recognition of ACE2 receptor, which is also highly expressed in the intestine.[42,43] Generally speaking, virus infection can damage the intestinal mucosa, destroy the digestion and absorption function of the intestine, affect the absorption of water by the intestine, and lead to enteritis. Recent studies have also shown that GI symptoms may be more common than initially thought. On the one hand, human intestinal epithelial cells are highly sensitive to the virus and can maintain a strong replication of the virus.[44] On the other hand, coronavirus has a tendency to the GI tract, which may be the reason for the frequent diarrhea of its infected people. There was evidence that SARS-CoV-2 RNA can be detected in the feces of nearly half of COVID-19 patients.[38] This showed that SARS-CoV-2 has also been found to increase the risk of GI diseases such as IBD in COVID-19 patients, due to its active infection and replication in the GI tract.[45] The incidence of severe COVID-19 was significantly higher in patients with GI symptoms (23%) than in patients without GI symptoms (8%), which is consistent with the hypothesis that the intestinal manifestations of COVID-19 may increase IBD symptoms.[46] Although there are some reports about the development of IBD in COVID-19 clinic, further research is needed to explore whether the association between IBD and COVID-19 is inevitable or coincidental.

3.2 | Can IBD increase the risk of COVID-19 infection?

Recent studies have found that immune-mediated inflammatory diseases may increase the risk of COVID-19 infection. Seven

case-control studies of COVID-19 indicated that patients with immune mediated inflammatory diseases are more likely to develop severe SARS-CoV-2 infection than the general population. The extent of alveolar tissue destruction and systemic lymphocytic infiltration are more severe, which means they have a more bleak prognosis. This may be due to their immune dysfunction and the use of immunosuppressive agents.[47,48] UC mainly involves the rectum and sigmoid colon, CD is more common in the terminal ileum and adjacent rectum, and ACE2 is highly expressed in intestinal epithelial cells at the end of the ileum, but its expression level is low in the colon. This may be one of the reasons why UC patients often have mucosal inflammation and are associated with a higher risk of COVID-19.[49–51] UC may affect lung function to some extent. A study of IBD patients diagnosed with COVID-19 in Italy found that factors associated with an increased risk of COVID-19 included age over 65 and active IBD.[52] This may be related to abnormal intestinal immune response during IBD activity, the infiltration of neutrophils, lymphocytes, plasma cells, and eosinophils in the lamina propriety of the intestinal mucosa, and the disorder of cytokine secretion. At the same time, the literature points out that about 30% of IBD patients are older than 65 years old,[53] combined with the disruption of active IBD to COVID-19, there is a possibility that IBD patients are susceptible to COVID-19. Taking into account clinical manifestations of most COVID-19, it is necessary to mention the increased risk of SARS-CoV-2 infection in IBD patients and an exacerbation of COVID-19.

3.3 | Can IBD worsen COVID-19 outcomes?

The study found that COVID-19 patients combined with IBD had a higher incidence of diarrhea, abdominal pain, endoscopic active diseases, and elevated biomarkers than non IBD patients in the control group.[54] The concentration of serum IL-6 in patients with diarrhea was higher, which increased the possibility of more severe systemic inflammation in this group. Brnne et al.[55] reported 525 patients from 33 countries and pointed out that old age, multiple complications and the use of immunosuppressants can worsen the infection of IBD patients and lead to poor prognosis. The choice of treatment has become the main determinant of the prognosis of COVID-19 in IBD patients. As for whether the application of immunosuppressants in IBD patients will aggravate COVID-19 infection, it is meaningless to ignore the type and dose of any drug and discuss the prognosis. Accumulating data suggested that systemic corticosteroid use was associated with the highest risk of severe outcomes of COVID-19.[53,56–58] High dose corticosteroid therapy has been identified as a risk factor for worse COVID-19 outcomes in the New York City cohort of IBD and other autoimmune diseases.[59] And in the study of using glucocorticoids to test patients with MERS and SARS, receiving high-dose glucocorticoids delayed virus clearance.[46] The use of anti-TNF or thiopurines was not associated with the development and prognosis of COVID-19 infection in a large retrospective cohort of IBD patients.[60] Interestingly, in a study by Lukin et al.,[54] the number of deaths and intensive care unit (ICU) admissions in the IBD group were lower than those in the control group. This suggests that some IBD drugs may lead to the weakening of cytokine release syndrome, resulting in more favorable results.

4 | MECHANISTIC SIMILARITY BETWEEN SARS-COV-2 INFECTION AND IBD

4.1 | ACE-dependent pathway

ACE is a dipeptidase dependent on chlorine and zinc, which plays an important role in fluid and electrolyte balance, blood pressure regulation, cardiovascular system development, and vascular remodeling.[61] On the one hand, it can cut angiotensin I (Ang-I) to produce angiotensin II (Ang-II), an effective vasopressin peptide; On the other hand, it can inactivate bradykinin, a protective factor for dilating blood vessels. In contrast, ACE2, a homologue of ACE, can inactivate Ang-II and convert it into angiotensin 1–7 (Ang-(1–7)). ACE2 is a negative regulator of ACE and has the effects of anti-inflammatory, antifibrosis, antiapoptosis, antiproliferation, and vasodilation.[62] ACE and ACE2 complement each other and antagonize each other. They are two key enzymes in the synthesis of bioactive components of the renin angiotensin system (RAS), which is an important body fluid regulation system in the human body and exists in the blood vessel wall, heart, kidney and other tissues and organs. In the two regulatory pathways of RAS (ACE/ANG-II/AT1R axis and ACE2/Ang-(1–7)/Mas R axis), ACE axis promotes inflammatory response and is anti-regulated by ACE2 axis in most inflammatory diseases.[62] In recent years, it has been found that ACE, ACE2 and their polypeptides played a vital role in the inflammatory process of myocardial hypertrophy, pulmonary hypertension, glomerulonephritis, lung injury, sepsis and acute pancreatitis.[62] Therefore, the balance between the two RAS axes is significant in inflammatory regulation. The development and prognosis of immune inflammatory diseases may be closely related to ACE/ACE2 imbalance.[63]

ACE2 is widely expressed in the lung and is the main natural receptor of SARS-CoV-2 spike. When SARS-CoV-2 enters cells through ACE2 receptor, it will lead to the downregulation of ACE2. The study found that ACE2 had a certain protective effect on acute lung injury, while other components of RAS, including ACE, Ang-II and Ang-II type 1A receptor (AT1a), could damage lung function and induce pulmonary edema.[64–66] Zou et al.[67] explored the potential risk of SARS-CoV-2 infection of different organs according to the ACE2 expression in it. ACE2 content of more than 1% was defined as high-risk tissues, including ileum (30%), heart (>7.5%), lower respiratory tract (2%), lung (>1%), esophagus (>1%), etc. The content of ileal part was significantly higher than that of other tissues in vivo, suggesting that ileal cells are highly susceptible to SARS-CoV-2. Because the content of ACE2 can regulate the immune inflammatory response to a certain extent, the immune inflammatory diseases acting on the ileum, such as IBD, may be affected by COVID-19 interfering with ACE2. Meanwhile, the mouse model constructed by burgueño et al.[68]

showed that ACE2 was highly expressed in intestinal epithelial cells of C57BL/6 mice, but inflammation could lead to the downregulation of ACE2 in epithelial cells. Therefore, we reasonably put forward a conjecture: on the one hand, pulmonary infection of COVID-19 patients downregulated the expression of ACE2, and the invasion of ileal cells is more serious and lasting than other parts. Lack of ACE2 protection may induce the occurrence and activity of IBD. On the other hand, immunohistochemical analysis showed that the average expression of ACE2 protein in the plasma of IBD patients was higher than that of the control group, and the plasma ACE2/ACE ratio was significantly higher than that of non IBD patients.[50,69] The increase of ACE2 in IBD patients may lead to a further increase in the risk of SARS-CoV-2 infection (Figure 1).

There is also evidence that in the active stage of IBD, the colonic mucosal lamina propria is diffusely infiltrated by neutrophils, lymphocytes, plasma cells, and eosinophils, and mucosal erosions and ulcers can be seen. In patients with COVID-19, a large number of infiltrating plasma cells and lymphocytes and interstitial edema were also seen in the stomach, duodenum, and rectal lamina propria. The same pathological signals in the GI tract suggest that COVID-19 can activate mucosal immune cells, leading to intestinal tract edema, inflammation and immune imbalance, thereby induce IBD.[70] ACE2 activator has been shown to exert a dual benefit in COVID-19 treatment, it can inhibit the binding of the S protein to ACE2 while providing protection for the ACE2 enzyme.[71] On the other hand, ACE2 activation is also beneficial in IBD, it can attenuate inflammation, oxidative stress and apoptosis, reduce synovial tissue migration, and dilate blood vessels. Activation of the negative regulator ACE promotes an increase in Ang-II, which may be pathologically associated with COVID-19 and IBD. In the inflammatory immune microenvironment, Ang-II alters vascular permeability by enhancing prostaglandin and vascular endothelial growth factor production.[72] These inflammatory mediators further support the activation of nuclear factor κ-light chain enhancer of activated B Cells (NF-κB), which is involved in cellular responses to external stimuli, enhances inflammatory responses and promotes inflammatory cell infiltration into damaged tissues.[72] In addition, the proliferation and activation of lymphocytes in leukocytes and the formation of free radicals also

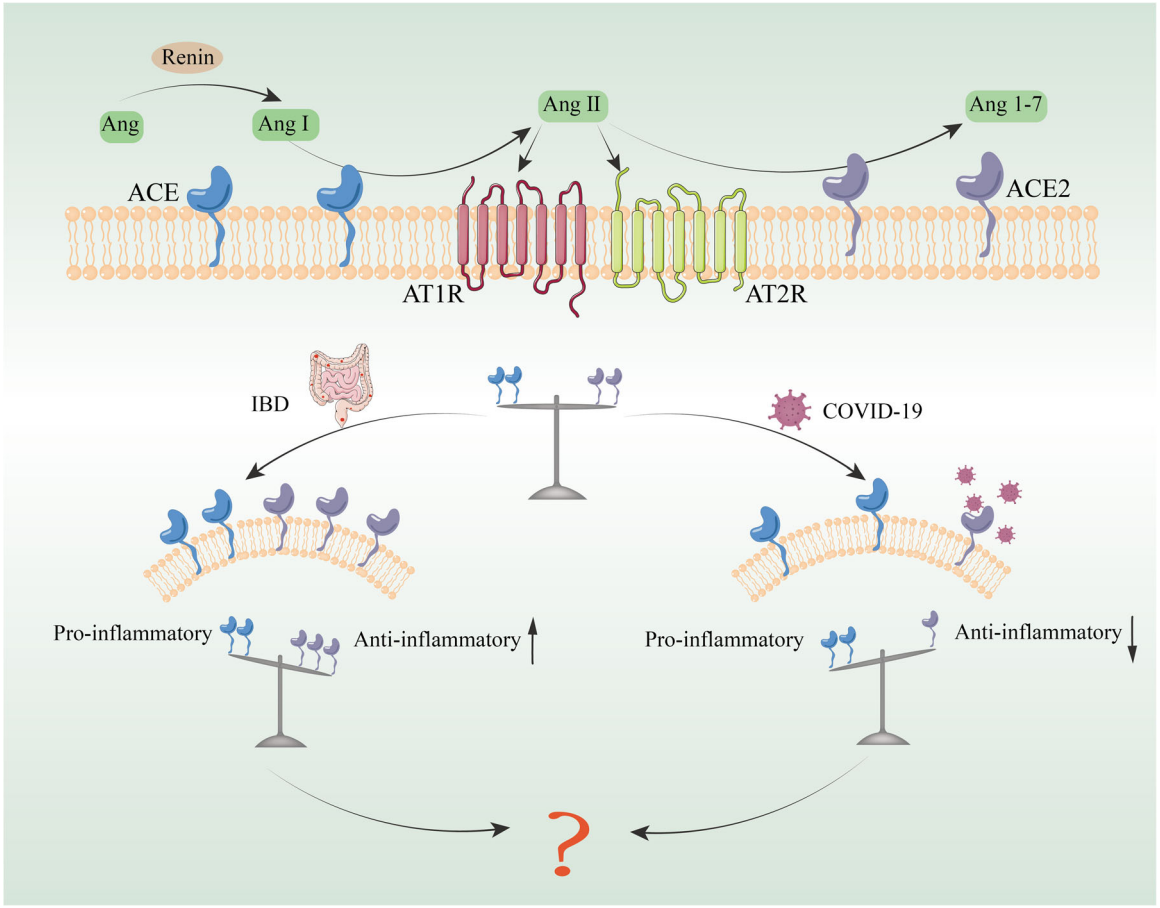

FIGURE 1 The imbalance of ACE and ACE2 in IBD and COVID-19 patients. Under normal circumstances, ACE and ACE2 in the renin-angiotensin system maintain a balance. Both SARS-CoV-2 and IBD can disrupt the balance, whether one disease affects the other is still inconclusive. We speculate that the downregulation of the protective factor ACE2 by COVID-19 may aggravate the original intestinal inflammatory response in IBD patients; the upregulation of the SARS-CoV-2 receptor ACE2 by IBD may induce the body's susceptibility to COVID-19. ACE2, angiotensin converting enzyme 2; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

depend on Ang II.[73] ACE inhibitors have been shown to provide a relatively safe and cheap option for the maintenance treatment of IBD.[74] It activates ACE2, delays the binding of SARS-CoV-2, increases the availability of Ang-(1–7) and inhibits NF-κB which is activated to limit the production of proinflammatory cytokines.[71] This antiinflammatory regulatory mechanism can effectively fight COVID-19 and IBD.[75] Therefore, COVID-19 and IBD may both mediate immune pathogenesis through abnormal ACE/ACE2 activity.

4.2 | IL-17-dependent pathway

IL-17 can be produced by cells on the mucosal surfaces of the skin, oral cavity, lung and GI tract, it can modulate protective immunity against extracellular pathogens by keeping barrier integrity, activating antimicrobial factors, and promoting granulocyte production.[76,77] IL-17 itself can only induce a weak inflammatory response, but IL-17 can cooperate with other cytokines to recruit and maintain inflammatory cells, thereby resulting in a strong inflammatory effect. By regulating the expression of chemokine ligands, granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF), these inflammatory cells are easier to enter the tissue.[77,78]

A series of pulmonary inflammation caused by COVID-19 is related to cytokine storm, which is characterized by elevated levels of IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, interferon (IFN)-γ, TNF-α, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)−1A, MIP-1B, etc. A significant corroboration of this is that the levels of these proinflammatory substances were higher in ICU patients compared with non-ICU patients. Most importantly, many of these proinflammatory substances, represented by cytokines, are associated with Th17 cells. For instance, IL-1β and TNF-α both promote Th17 responses and vascular permeability and leakage. Conversely, Th17 cells also exert broad proinflammatory effects by inducing the production of cytokines IL-17, GM-CSF, G-CSF, IL-1β, IL-6, TNF-α.[79] Moreover, there are some more direct evidence that the Th17 cells are involved in COVID-19 pathogenesis. A large number of Th17 lymphocytes were detected in the first anatomopathological lung analysis. Xu et al.[80] revealed a very high number of CCR6+ Th17 cells in the peripheral blood of a critically ill COVID-19 patient, further supporting the existence of a Th17-type cytokine storm in the disease. Th17 cells are known to be involved in host defense against extracellular pathogens and the occurrence of autoimmune and inflammatory disorders, such as multiple sclerosis, rheumatoid arthritis and IBD.[81,82]

The expression levels of IL-17 in peripheral blood and intestinal mucosa of patients with active UC and CD were significantly higher than those of healthy controls.[83,84] Fujino et al.[85] did not detect IL-17 in the serum of normal people, patients with infectious colitis and patients with ischemic colitis, but observed a remarkable increase in the level of IL-17 in the serum of patients with IBD. This finding suggests that IL-17 might be involved in the pathogenesis of IBD and is a characteristic factor of IBD. In a study of UC animal model by Ito et al,[86] the inactivation of IL-17 could lead to a lighter course of the disease. The level of IL-17 might affect the progression of IBD. Furthermore, increased abundance of Th17 cells in patients with active IBD was correlated with disease activity index and endoscopic histological score.[87] These results provide evidence for the momentous role of Th17 cells and Th17-related cytokines (IL-17A, IL-17B, and IL-22) in IBD mucosal injury and disease activity.

Cytokine storms caused by COVID-19 infection can produce a large amount of IL-17, which can also be observably upregulated in patients with IBD. The upregulation of IL-17 expression may induce severe COVID-19 infection or IBD activity, which shows that the upregulation of IL-17 in patients with either COVID-19 or IBD will lead to the aggravation or susceptibility of the other. In COVID-19 and IBD, excessive stimulation will lead to overproduction of IL-17, thereby participating in proinflammatory pathological activities. On the one hand, IL-17 can promote the production of eosinophils in the bone marrow and their migration and accumulation to target organs, and then mediate cytokine storm on the basis of lung and GI injury. On the other hand, IL-17 can promote the replication of some viruses by enhancing the virulence of the virus, accelerating the progress of acute lung injury and destroying the intestinal microecology (Figure 2).

4.3 | Shared genetic etiology between COVID-19 and IBD

After SARS-CoV-2 infection, there are different clinical outcomes among individuals, which can be manifested as asymptomatic infection, mild pneumonia, and severe pneumonia according to the condition.[77] On the one hand, the diverse clinical outcomes of different individuals infected with SARS-CoV-2 are caused by various factors such as gender, age, and underlying diseases among individuals,[88] on the other hand, a number of recent genetic association studies of COVID-19 have shown that the development of COVID-19 may be an integrated manifestation of the complex interactions among microorganisms, environment and host genetic components, and the genetic factors of the body play an important role in the infection and progression of COVID-19.[89–93]

Differences in susceptibility genes among different countries suggest that the genetic susceptibility to severe COVID-19 is population-specific. Zhang et al.[94] found that loss-of-function genetic variants on the IFN pathway were significantly enriched in severe COVID-19 patients, while the IFN receptor gene *IFNAR2* was present at the 21q22.1 locus, consistent with the UK study.[90] The study by Langer et al.[95] showed that IFN-γ played a pathogenic role in IBD by disrupting the adhesion junction protein VE-cadherin, causing the breakdown of the vascular barrier. Moura et al.[96] found that DNA methylation sites were epigenetic susceptibility sites for respiratory failure in critically ill patients. Although there was no direct evidence that DNA methylation is a susceptibility factor of IBD, an individual who has inherited a set of normal DNA may still suffer from IBD in the

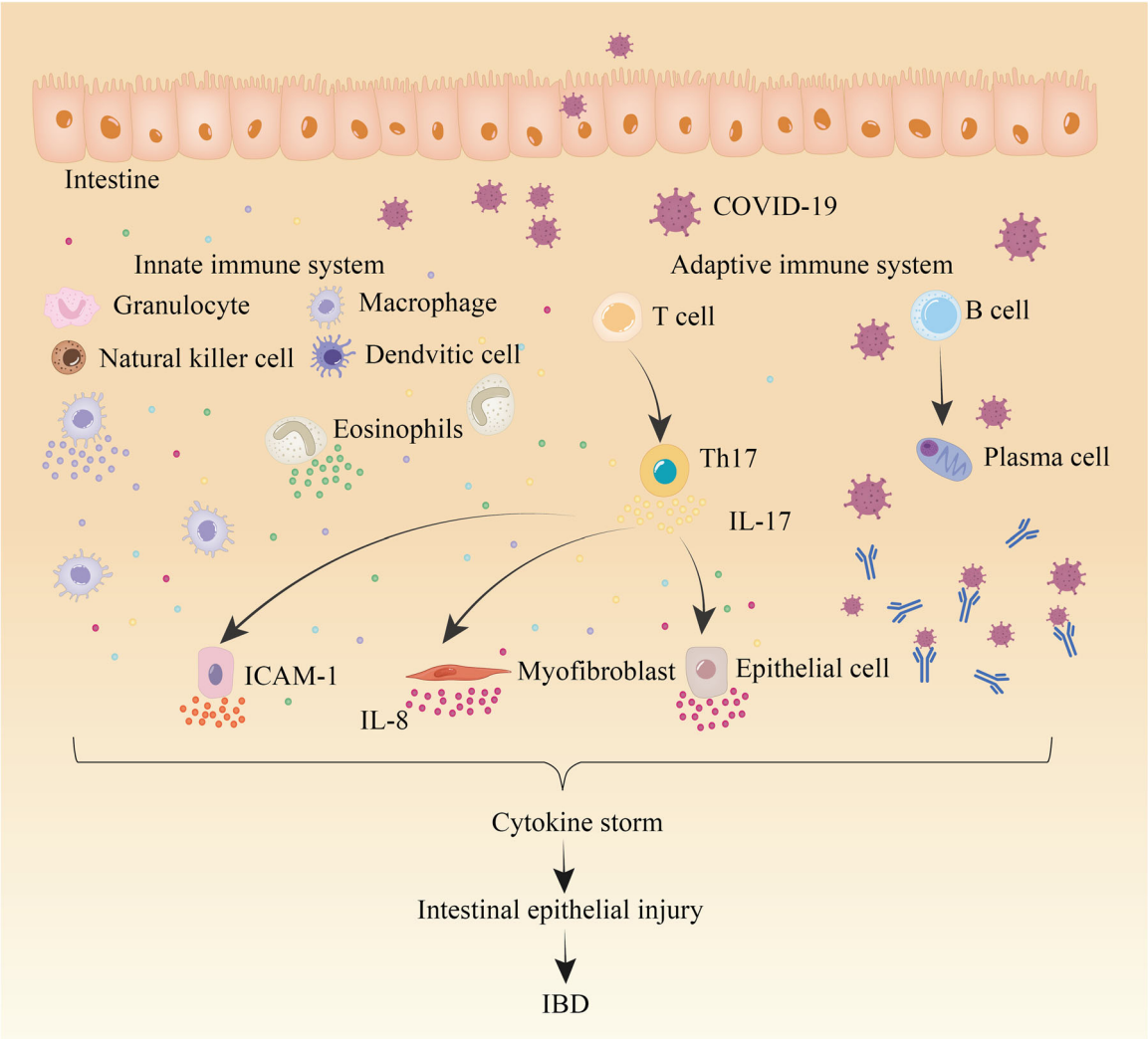

FIGURE 2 The immune storm caused by the infection of SARS-CoV-2 may induce or aggravate IBD. After SARS-CoV-2 invades the gut, it causes excessive activation of immune cells in the innate immune system and the adaptive immune system. Through a cascade reaction, excess cytokines are produced, triggering a cytokine storm, in which IL-17 secreted by Th17 cells is used throughout the played an important role in the process. The release of various proinflammatory mediators leads to intestinal epithelial injury, which can induce or exacerbate IBD. IBD, inflammatory bowel disease; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

subsequent growth process, suggesting that it may be related to epigenetic changes in the whole life cycle, such as DNA methylation.[97]

Indirect evidence suggests that methylation effect may play an important role in the pathogenesis of IBD. The heritability of UC is 33% and that of CD is 30.5%, which are related to single-nucleotide polymorphism affecting methylation level.[98] In addition, COVID-19 activates the immune inflammatory response, causing the cytokine storm to produce a large amount of IL-17, which is also involved in gene regulation. Nishida et al.[99] found that the *IL17A/IL17F* gene was a novel susceptibility gene associated with COVID-19 severity, and it was also involved in various diseases including IBD.[100] These biomarkers, combined with other genetic factors, may contribute to the early detection, early prediction, early intervention and clinical stratified management of COVID-19 patients; at the same time, they play a suggestive role in the genetic co mutation of COVID-19 and IBD.

5 | THERAPEUTIC MANAGEMENT AND CHALLENGES

5.1 | Challenges and recommendation of IBD drugs in the COVID-19 setting

IBD patients exhibit compromised immune systems that make them more susceptible to SARS-CoV-2 infection. Immunosuppressive therapy may mitigate the adverse effects of IBD, but may further increase the risk of SARS-CoV-2 infection. In addition, the symptoms of active IBD and the clinical features of SARS-CoV-2 infection often overlap, and an increasing number of case reports have found coexistence of IBD with COVID-19. In IBD patients, a large number of symptoms are similar to the digestive system manifestations of COVID-19, including loss of appetite, diarrhea, nausea, vomiting, abdominal pain, fever, etc.[1,101] In fact, IBD patients are often associated with mutiple

comorbidities, such as arthropathy, thromboembolism, pulmonary inflammation, etc.[102] Several studies have shown that even in the absence of respiratory symptoms, 40%–60% of IBD patients have impaired lung function and impaired diffusing capacity.[103]

Therefore, clinical management of IBD is a challenging task in the current COVID-19 environment. The greatest risk is not only related to the infection itself, but also to the urgent restructuring of hospitals and general practice services, which will lead to major changes in routine IBD services. Currently, the restrictions on outpatient admissions due to the epidemic mainly bring the following problems to IBD patients: (1) Patients who regularly use biologics cannot continue to be admitted to the hospital regularly for treatment, and certain drugs cannot be obtained in a timely manner; (2) Endoscopy review cannot be performed; (3) Surgical arrangements are restricted.

Among them, how to use drugs rationally during the COVID-19 pandemic is the most concerning issue for IBD patients. The British Society of Gastroenterology (BSG) agrees with the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) and the European Crohn's and Colitis Group that patients should continue their current medication and do not recommend reducing or discontinuing their medication.[104–106] Because the flare-up may lead to the need for steroids or other additional immunosuppression or hospitalization. Nonetheless, a direct association between specific IBD medications and the development or outcome of COVID-19 has not been established, but patients with IBD may be at an increased risk of serious infections.

Accumulating evidence suggest that immunosuppression is the main way of the protective effect of glucocorticoids against COVID-19, which reverses the late stage of SARS-CoV-2 infection by reducing the ability of immune cells to recognize and clear foreign bodies.[107] The World Health Organization recommends glucocorticoid therapy for severe/critical COVID-19 cases.[105] However, high-dose steroids is a risk factor for respiratory and opportunistic infections in IBD.[108,109] Therefore, even in COVID-19-positive cases, glucocorticoids are recommended to be used with caution and at the lowest possible dose for a short period of time, and abrupt discontinuation is discouraged. For immunomodulators, although there is currently no clear evidence of increased risk of SARS-CoV-2 infection. However, in older patients (>60 years) or those with severe comorbidities, thiopurine discontinuation may wish to be considered. Continuation of injectable therapy (infliximab, vedolizumab, ulinatinib, adalimumab, certolizumab, and golimumab) has been proposed, regardless of patient risk category and isolation recommendations.

5.2 | GI symptoms after vaccination

COVID-19 drug treatment is mainly to avoid serious complications. So far, there is no specific antiviral drug for SARS-CoV-2 infection. The outbreak and persistence of COVID-19 epidemic highlight the importance of vaccines and the urgent global demand for vaccines. At present, there are many registered vaccines, and other vaccines are also being developed.[110,111]

Inactivated vaccines, adenovirus-vectored vaccines, and messenger RNA vaccines are the three shining stars of the vaccines that have come out, they have played an indelible role in the prevention and control of COVID-19 worldwide. However, just as every coin has two sides, vaccinations are not all benefits and no harm. In the era of large-scale vaccination against COVID-19, although it is a small-probability event, allergic reactions have been widely reported as adverse results after vaccination, and most of them are skin manifestations such as diffuse erythema and extensive systemic urticaria,[112] also often accompanied by dyspnea, nausea, vomiting, abdominal pain, swollen lips, etc.[112–114] In addition, more serious diseases such as autoimmune hepatitis,[115] acute pancreatitis,[116] acute myocarditis,[117] immune thrombotic thrombocytopenia (VITT),[118] and multisystem inflammatory syndrome[119] have also been reported. If not treated in time, it may lead to DIC, shock, and even death. It can be seen from a large number of case reports around the world that abdominal pain, nausea, vomiting and other digestive system symptoms are relatively common in adverse reactions. Most of the symptoms are mild, and most of them can be relieved, and the prognosis is good. Severe, life-threatening acute illness after vaccination is mostly associated with explosive immune dysregulation.

Although a number of international organizations have pointed out the feasibility of vaccinating patients with IBD against COVID-19, as an immune disease of the digestive system, the patient's own immune function is more fragile than that of the normal population, and is more susceptible to external interference. Symptoms and their frequency, severity, and duration following initial SARS-CoV-2 vaccination in IBD patients were similar to those in the general population. An observational cohort study reported that the incidence of GI symptoms in patients with IBD after the third dose was 8.8%, slightly higher than the 7.8% after the second dose.[120] Vaccines, as an antigen, form antigen-antibody complexes with specific antibodies produced in the body after vaccination, and play a preventive role against infectious diseases. However, vaccines stimulate the innate immunity of the host's immune defense mechanism, and in the process of inducing the development of specific and acquired immunity, the host's immune function may be disturbed, and many adverse reactions may occasionally occur.[121]

5.3 | Feasibility of COVID-19 vaccine in IBD patients

In general, inactivated vaccines for COVID-19 are considered safe in IBD patients, regardless of the treatment for IBD. However, vaccine prophylaxis may be less effective in IBD patients, due to autoimmune disorders or the use of certain types of immunosuppressants, such as high-dose corticosteroids (≥20 mg prednisolone or equivalent drugs), immunomodulators, anticytokine therapy (including anti-TNF and anti-IL-12p40 drugs), anticytokine therapy (Vedolizumab) and a small molecule signaling inhibitor (Factoinib).[122–125] This is also the most critical consideration for IBD patients when deciding whether to

vaccinate against the SARS-CoV-2. Because IBD patients were excluded from phase 3 clinical trials of approved vaccines, data on the side effects of vaccination and the risk of disease activation are lacking. Previous experience vaccinating patients with IBD against infectious diseases such as pneumococcus, hepatitis A virus, hepatitis B virus, and influenza suggests that immunosuppressive therapy may impair the immune response to vaccines and reduce the effectiveness of the immune process.[126] Nevertheless, the risk of vaccination in patients with IBD is relatively low and IBD should not be a contraindication to the vaccine.

With vaccine rollout and feedback on good preventive effects, an expert panel from the IOIBD recommended that all patients with IBD should be vaccinated as soon as they can, regardless of immunomodulatory therapy. The exception is live attenuated virus vaccines or replication-competent viral vector vaccines. Meanwhile, IBD patients should be vaccinated based on their overall risk of exposure to SARS-CoV-2 and their risk of complications[127] The UK Joint Committee on Vaccination and Immunization and The BSG also noted that for most patients, active IBD should not be a barrier to vaccination.[126] Partial evidence also confirms that the timing of annual influenza vaccination does not significantly affect vaccine immunogenicity.[128] A large number of authoritative institutions have conveyed a core point to us: the risk of SARS-CoV-2 vaccination is completely controllable, and the benefits of SARS-CoV-2 vaccination for IBD patients outweigh the disadvantages.

5.4 | Monitoring and nursing of IBD patients in the COVID-19 setting

In the ongoing COVID-19, the monitoring and nursing of IBD patients is a major challenge for experts. During the period of COVID-19, doctors are advised not to visit patients with SARS-CoV-2 infection regularly. Isolation during the COVID-19 epidemic also helps to solve this problem. Therefore, in the absence of routine clinical assessment of face-to-face communication between physicians and patients, it is indeed a challenging task for physicians to follow an effective disease control program to mitigate IBD activity. In this case, doctors need to develop more appropriate strategies to provide the best care for patients.

Recent reports showed that telemedicine was becoming more and more popular in this situation.[129] It supports online consultation for patients with stable conditions, and reduces the number of doctor visits and avoids the risk of contact with the outside world through a virtual consultation with doctors. In India, doctors prefer voice-over-IP services, followed by video consultations and email for virtual care.[130] It was also found that telephone consultation supported by supplementary information, such as laboratory tests and performance photos of suspected diseases, was also effective in avoiding physical examination.[131,132] Based on this, Barello et al.[133] produced the "WE-CARE IBD score," a short self-administered questionnaire including six items, which captures the needs of IBD patients and their own medical priorities, and evaluates the condition and nursing quality from the perspective of patients. However, these remote consultations do not allow proper clinical examination, which is essential for accurate diagnosis.

Since it is difficult to predict when the ongoing pandemic will end, experts will put forward some requirements for patients to consciously cooperate in treatment, such as nutrition should be optimized, because malnutrition will destroy the innate immune response, including the formation of complement and mucosal secretory antibodies.[134] Smoking is associated with worse outcomes and higher mortality of COVID-19,[135] so patients should be encouraged to quit smoking. Vaccination should be strongly encouraged to prevent co-infection with other viruses. IBD patients should maintain social distance at work, preferably more than 2 m away from others, avoid touching the nose, eyes and mouth, and avoid unnecessary travel.[130,131] In general, patients with stable disease activity may be advised to reduce the number of visits and use a virtual platform to demonstrate disease activity when necessary. For IBD patients with COVID-19, who need frequent medical visits due to severe illness or other treatment requirements, all precautionary measures may be recommended in emergency situations to avoid infection or stop infection (for new pneumonia-positive patients).[136]

6 | PERSPECTIVE

Increasing evidence suggests that some key pathways and mediators may be central hubs in the regulation between COVID-19 and IBD. Recent studies have shown that the intestinal tract has host specific symbiotic colonization, and the colonizing flora played a key role in the occurrence and development of intestinal diseases. The intestinal microbiota has the ability to affect different physiological aspects, such as human nutrient absorption, resistance to foreign pathogens, participation in metabolism, regulation of immune and inflammatory responses, etc. In addition, the microbiota has also been demonstrated to be a major player in autoimmunity, and changes in its composition may lead to a loss of immune tolerance.[137,138] Yeoh et al.[139] found that the composition of gut microbiota in patients with COVID-19 could reflect the severity of the disease and immune dysfunction. Coincidentally, according to a study by Johnson et al.,[140] the imbalance of flora is related to local inflammatory reaction (especially Th17 responses) and high circulating levels of anti-double-stranded DNA and histone antibodies. The gut microbes can directly affect COVID-19 and immune system diseases, such as IBD; they can also indirectly participate in the regulation of the two diseases by regulating IL-17. Therefore, bidirectional cross-linking of the gut microbiota plays a crucial role in various systemic diseases and may be a promising therapeutic target for these diseases. However, whether the dysbiosis of the gut microbiota causes immune abnormalities; whether the disease causes the invasion of foreign microorganisms or the change of the original flora is still at the stage of debate. This may be an interesting and promising research direction with broad prospects.

7 | CONCLUSIONS

With emerging evidence that IBD and COVID-19 share similar pathological mechanisms in affected tissues and overlapping clinical manifestations, two pathways, ACE/ACE2 and IL-17, have been found to be potential coregulatory targets for COVID-19 and IBD. In the context of the COVID-19 epidemic, the treatment and care strategies for IBD patients is a challenging task. Considering the severity of the disease and appropriate risk-benefit studies, in general, the benefits outweigh the risks of using IBD medications and vaccination during the COVID-19 pandemic, and implementing individualized clinical monitoring of IBD patients will be the best treatment strategy for effective disease control. Virtual counseling is recommended for patients with stable course control of IBD during the pandemic, while patients with flare-up IBD are advised to take all precautions during their visit to prevent SARS-CoV-2 infection.

AUTHOR CONTRIBUTIONS

Hai-Feng Pan, Zong-Wen Shuai and Jing Ni: conceived the idea and proofread the manuscript. **Sha-Sha Tao**: drafted and revised the manuscript. **Xin-Yi Wang and Xiao-Ke Yang**: participated in literature search and information collection. **Yu-Chen Liu, Zi-Yue Fu, Li-Zhi Zhang and Zhi-Xin Wang**: participated in chart making and language editing. All authors have read and approved the submitted version for publication.

ACKNOWLEDGMENTS

This study was funded by grants from the National Natural Science Foundation of China (81872687), Anhui Provincial University Natural Science Research Project (KJ2021A0230), Anhui Provincial Natural Science Foundation (2108085Y26, 2108085QH361).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Tao S-S, Wang X-Y, Yang X-K, et al. COVID-19 and inflammatory bowel disease crosstalk: From emerging association to clinical proposal. *J Med Virol*. 2022;1-13. doi:10.1002/jmv.28067