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Altered gut microbiota patterns in COVID-19: Markers for inflammation and disease severity

Chakraborty C *et al*. Gut microbiota in COVID-19 patients

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to a severe respiratory illness and alters the gut microbiota, which dynamically interacts with the human immune system. Microbiota alterations include decreased levels of beneficial bacteria and augmentation of opportunistic pathogens. Here, we describe critical factors affecting the microbiota in coronavirus disease 2019 (COVID-19) patients. These include, such as gut microbiota imbalance and gastrointestinal symptoms, the pattern of altered gut microbiota composition in COVID-19 patients, and crosstalk between the microbiome and the gut-lung axis/gut-brain-lung axis. Moreover, we have illustrated the hypoxia state in COVID-19 associated gut microbiota alteration. The role of ACE2 in the digestive system, and control of its expression using the gut microbiota is discussed, highlighting the interactions between the lungs, the gut, and the brain during COVID-19 infection. Similarly, we address the gut microbiota in elderly or co-morbid patients as well as gut microbiota dysbiosis of in severe COVID-19. Several clinical trials to understand the role of probiotics in COVID-19 patients are listed in this review. Augmented inflammation is one of the major driving forces for COVID-19 symptoms and gut microbiome disruption and is associated with disease severity. However, understanding the role of the gut microbiota in immune modulation during SARS-CoV-2 infection may help improve therapeutic strategies for COVID-19 treatment.

Key Words: COVID-19; Inflammation; Gut microbiota; Therapeutic

Chakraborty C, Sharma AR, Bhattacharya M, Dhama K, Lee SS. Altered gut microbiota patterns in COVID-19: Markers for inflammation and disease severity. *World J Gastroenterol* 2022; In press

Core Tip: The gut microbiota of coronavirus disease 2019 (COVID-19) patients is altered compared to that of healthy individuals, with a reduction in the count of beneficial bacteria and an increase in the count of opportunistic fungi. In this review, we elucidate the components governing immune modulation. Additionally, we explore the effect of changes in the microbial ecosystem in COVID-19 patients, with an aim to help develop precise therapeutics and expand our knowledge regarding the pattern of changes in the gut microbiota of COVID-19 patients.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has stimulated research on several medical conditions and on individual patient variations during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to unfold underlying disease mechanisms. Scientists have determined the inflammatory response and cellular injury mediated by acute SARS-CoV-2 infection. Moreover, several studies have revealed the involvement of the gastrointestinal (GI) tract and its associated gut microbiome during COVID-19, motivating research in this field. Increasing evidence has surfaced confirming the association of the GI tract and COVID-19, including[1,2] a severe state of gut dysbiosis in COVID-19 patients[3,4]. Similarly, GI symptoms such as vomiting, abdominal pain, and diarrhea have been noted in many COVID-19 patients[5-7]. Moreover, high expression of ACE2 receptor was reported in epithelial cells of the GI tract[8]. SARS-CoV-2 RNA has been identified in rectal and anal swabs, as well as stool specimens[7,9-10]. Finally, liver damage, loss of appetite, and irritable inflammatory diseases have been reported as post-COVID-19 illnesses[11]. These all data strongly indicate a correlation between the GI including the gut microbiome, and COVID-19.

The gut microbiota plays an important role in controlling gut health and acts as a health modulator (Figure 1)[12] aidings in different metabolic activities and

extensively impactings health and disease[13,14]. Ongoing research aims to better understand the gut microbiota and provide insights into the mechanistic conditions required to implement normal health functions. The gut microbiota controls specific functions in the host, such as drug and xenobiotic metabolism and nutrient metabolism[15]. Simultaneously, it helps maintain the structural integrity of the gut mucosal barrier, protects against pathogens, and regulates immunomodulation, as well as health and disease conditions[16,17]. Several other studies suggest a possible link between COVID-19 and gut microbiota composition[18,19]. Additionally, an association has been shown between altered gut microbial composition and increased risk factors in COVID-19 patients (Figure 1)[20,21].

Inflammation is a major risk factor in COVID-19 patients[22-24]. During uncontrolled inflammation, abnormal levels of cytokines such as interleukin-1 beta (IL-1β), IL-6, IL-8, IL-10, IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) are found in the patients[23,25-27]. Certain abnormal levels of cytokines are substantial related to the severity of COVID-19 and are probably responsible for the "cytokine storm" syndrome manifested during the disease[28-30]. Research has correlated the inflammation during COVID-19 with GI and hepatic manifestations of the disease[31].

Interactions between the gut microbiota and the lungs, known as the gut-lung axis, have sparked interest for gastroenterology studies focusing on COVID-19 as these interactions affect disease severity. Changes in the gut microbiome certainly affect homeostasis and may lead to increased infections[32,33]. Similarly, in addition to the gut, COVID-19 can also have a detrimental effect on the central nervous system (CNS) and the blood-brain barrier (BBB) and disrupt the gut-brain-lung axis. Studies have explored therapeutic options (nicotinic cholinergic agonists and vagus nerve stimulation) to minimize the damage caused to this axis[34].

Research is necessary to understand how the gut microbiome is altered during COVID-19 infection and the factors that influence the microbiome during mild to moderate and severe disease. Studies have been conducted to understand the GI symptoms during COVID-19 and to detect viral shedding using the fecal matter of SARS-CoV-2 patients. The gut microbiota of COVID-19 patients has been mapped to

obtain evidence regarding inflammation, disease severity, and therapeutic development.

Using these studies, we explore the following critical factors: (1) The gut microbiota imbalance and GI symptoms in COVID-19 patients; (2) fecal viral shedding in COVID-19 patients and restoration of the gut microbiota; (3) the pattern of altered gut microbiota composition in COVID-19 patients; (4) alterations in gut biosynthesis during COVID-19 infection; (5) the role of ACE2 in the digestive system and the gut microbiome; (6) crosstalk between the microbiome and the gut-lung axis during COVID-19 infection; (7) crosstalk between the microbiome and the gut-brain-lung axis during COVID-19 infection; and (8) hypoxia during COVID-19 associated with altered gut microbiota. We also discuss how immune responses and inflammation due to COVID-19 drive the changes in the microbial ecosystem and summarize therapeutic options currently in development.

GI SYMPTOMS IN COVID-19 PATIENTS

Along with respiratory symptoms and fever, GI symptoms have also been observed in COVID-19 patients (Table 1). A study by Redd *et al*[35] reported abdominal pain (14.5%), nausea (26.4%), diarrhea (33.7%), and vomiting (15.4%) in patients from the United States. Three hundred and eighteen hospitalized COVID-19 patients were evaluated to understand their symptoms. In another study with 204 COVID-19 patients, 50.5% (103 patients) exhibited GI symptoms. Among these 103 patients, 78.6% showed a lack of appetite, 34% had diarrhea, 3.9% vomited, and 1.9% complained of abdominal pain. The authors correlated patients describing GI symptoms with other measurements such as prothrombin time, monocyte count, and liver enzyme levels. Patients with GI symptoms had elevated mean liver enzyme levels, extended prothrombin times, and lower monocyte counts[36]. In a much larger cohort study involving 1099 COVID-19 patients from 552 different hospitals spread to over 30 provinces, only 3.8% of patients experienced diarrhea. The authors concluded that fever and cough are common symptoms, unlike diarrhea, among the COVID-19 patient population[37].

These findings suggest that the virus might be present for a period in the GI tract, which may cause a GI infection (Figure 2). Importantly, fecal viral shedding was noted after clearing SARS-CoV-2 from the respiratory tract, suggesting that the virus can persist for a long time in the GI tract, especially in patients who manifest GI symptoms. During COVID-19 infection, gut microbiota composition is altered, possibly explaining the GI imbalance and manifestations of the different GI symptoms such as abdominal pain, nausea, vomiting, and diarrhea, as described above. This change in the gut microbiota includes reduced levels of commensals microbes and is observed in patient samples even after 30 d of disease remission[38-40]. Additional studies addressed the imbalance of the gut microbiota and its association with different GI-related aspects of COVID-19[41]. The gut microbiota population in COVID-19 patients with low to moderate GI symptoms should also be analyzed. Evaluating these diverse patient populations will enable a thorough description of this phenomenon.

FECAL VIRAL SHEDDING IN COVID-19 PATIENTS

Table 2 lists various cohort studies reporting fecal viral shedding by COVID-19 patients and detecting SARS-CoV-2 RNA in the fecal matter[42,43]. SARS-CoV-2 RNA-positive fecal matter was detected in 66.67% of COVID-19 patients (42 patients) in China[43]. Researchers attempted to evaluate the viral shedding period in stool samples, and noted viral shedding in asymptomatic patients. For example, SARS-CoV-2 RNA was detected from a stool sample of an asymptomatic child 17 d after viral exposure[9].

Certain studies have reported that virus separation from stool samples is difficult. For example, Wölfel et al[44] detected viral RNA in stool samples but attempts to isolate the virus were unsuccessful, most likely due to the mild nature of the infection. A viral load below 10^6 copies per milliliter often hampers viral isolation[36]. The viral load also varies widely from one sample to another, including stool, serum, and respiratory samples[44-46]. However, understanding the correlation between the altered gut microbiota and the viral load in patient samples is essential for advancing therapeutic strategies centered around restoring the microbiota.

Additionally, efforts should focus on determining the possible correlation between fecal viral shedding and altered gut microbiota composition at different stages the infection, *i.e.,* mild to moderate or severe COVID-19.

ALTERED GUT MICROBIOTA COMPOSITION IN COVID-19 PATIENTS

SARS-CoV-2 infections have led to changes in the ecology of the gut microbiota in patients (compared to that seen in controls). These changes are influenced by the immune responses elicited during COVID-19 (Table 3). Different studies have revealed the growth of unusual microorganisms and depletion of common gut microbes (bacterial, viral, and fungal populations) in COVID-19 patients (Figure 3). To understand the severity of disease in COVID-19 patients, the gut microbiota composition of 100 COVID-19 patients was analyzed in two hospital cohorts. Stool samples were collected from 27 of the 100 patients. The gut microbiome compositions were characterized using total DNA extracted from stool samples. The authors demonstrated that the number of gut commensals and Bifidobacteria was low and correlated with several factors of disease severity, such as high concentrations of inflammatory cytokines and C-reactive protein (CRP). These data suggests that the composition of the microbiota is associated with disease severity[38]. Another study carried out RNA and DNA profiling by sequencing of the virome using fecal matter from COVID-19 patients. The fecal matter of 98 COVID-19 patients was analyzed to understand COVID-19 severity and its association with the gut virome. The study showed that COVID-19 severity is inversely correlated with gut viruses, and older patients are more prone to severe COVID-19 outcomes[47]. Alterations in fungal microbiomes during COVID-19 have also been investigated. Analysis of the fecal mycobiome using the deep shotgun method showed heterogeneous microbial profiles, with enrichment of fungal genera such as Aspergillus and Candida. Two species of *Aspergillus* (*Aspergillus flavus* and *Aspergillus niger*) were identified in fecal samples after clearance of SARS-CoV-2 from nasopharyngeal samples[48]. Additionally, there is evidence of abundant symbionts among COVID-19 patients including *Clostridium ramosum, Coprobacillus,* and *Clostridium hathewayi,* which directly correlated with disease severity.

Conversely, *Faecalibacterium prausnitzii,* which was also abundant among the patients, was inversely correlated with disease severity[49].

Similarly, in a study by Yeoh *et al*[38], stool samples from 27 patients were correlated with blood markers and inflammatory cytokines. The study concluded that the scale of COVID-19 severity might be associated with the gut microbiome and linked it to COVID-19 inflammation[46]. In another studycontaining a greater number of African Americans, enriched genera (*Campylobacter, Corynebacterium,* and *Peptoniphilus)* were mapped in the COVID-19 patient population, the gut microbial composition was markedly different between positive and negative samples. However, the study did not identify any considerable association between COVID-19 severity and microbiome composition[50].

Certain studies even noted a reduction in fiber-utilizing bacteria such as *Prevotella, Bacteroides plebius,* and *Faecalibacterium prausnitzii* (*F. prausnitzii*), and a low Firmicute/Bacteroidetes ratio[51]. Poor outcomes were noted in special populations, such as hypertensive, diabetic, and elderly patients[52,53]. Research is still underway to ascertain the different types of gut microbial populations (pro-inflammatory, opportunistic, beneficial, or anti-inflammatory) present depending on COVID-19 severity (Figure 4).

These studies help us understand how gut microbiota composition affects patients with moderate to severe COVID-19 and how gut microbiota diversity might alter immunity in COVID-19 patients.

ALTERATIONS IN THE BIOSYNTHESIS OF BIOLOGICAL COMPOUNDS IN THE GUT DURING COVID-19 INFECTION

Other than compositional changes in gut microbiota, functional changes during SARS-CoV-2 infection were observed in some patients. The gut microbiota aids in different biosynthetic pathways, such as amino acid biosynthesis, carbohydrate metabolism, nucleotide de novo biosynthesis, and glycolysis. This might be due to the abundance of bacterial components such as *Collinsella tanakaei, Streptococcus infantis, Morganella morganii,* and *Collinsella aerofaciens, etc.* Apart from these microbes, many short-chain fatty acid (SCFA) synthesis bacteria, such as

Lachnospiraceae bacteria, *Bacteroides stercoris, Alistipes onderdonkii,* and *Parabacteroides merdae* were present in COVID-19 samples with mild symptoms and in non-COVID-19 samples[54]. In a study using non-human primate models, β diversity analysis and 16S rRNA gene profiling were carried out to understand the gut microbiota composition during SARS-CoV-2 infection. The study revealed substantial changes in the gut microbiota composition and metabolism and a reduction in the concentration of SCFAs as well as a difference in the concentrations of bile acids. The study also found alterations in tryptophan metabolites during SARS-CoV-2 infection in the animal models[55].

Shotgun metagenomic sequencing using fecal samples has also been performed to profile the gut microbiome in SARS-CoV-2 infected patients. Researchers observed prolonged impairment of L-isoleucine biosynthesis and SCFAs due to alterations in the gut microbiome of patients with COVID-19[56].

ROLE OF ACE2 IN THE DIGESTIVE SYSTEM AND THE GUT MICROBIOME

The ACE2 (angiotensin-converting enzyme 2) receptor acts as a binding site by which SARS-CoV-2 enters host cells[57,58]. A higher expression of ACE2 in the cell favors SARS-CoV-2 infection. Despite this, ACE2 deficiency can play a vital role in SARS-CoV-2 infection[59]. Increased ACE2 expression is found in the epithelial cells of the respiratory tract (nasal mucosa, nasopharynx, and lungs), in different parts of the intestine, and in different types of epithelial cells, including nasal, corneal, and intestinal epithelial cells in humans[60]. In addition, this protein is expressed in different parts of the digestive system, such as the small intestine, stomach, colon, and liver[61]. However, ACE2 expression is controlled by distinct microbial communities in several body tissues. Mouse model studies suggest an association between certain microbial communities and overexpression of ACE2. This overexpression may prevent detrimental changes in hypoxia-induced gut pathophysiology and pulmonary pathophysiology[62]. ACE2 expression is controlled in the GI and respiratory tract[63]. Additionally, it can also be controlled by some bacterial species from important phyla. Downregulation of ACE2 expression was associated with the Bacteroidetes phylum. Among all species of this phylum,

Bacteroides dorei has been shown to inhibit ACE2 expression in the colon, whereas the Firmicutes phylum plays a variable role in its modulation[20,49,64]. These findings are supported by other studies describing the modulation of ACE2 expression in the gut by the microbiota[65,66].

GUT-LUNG AXIS CROSSTALK DURING COVID-19 INFECTION

Several reports indicate that manipulation of the gut microbiota may be used to treat pulmonary diseases[67]. Therefore, the gut-lung axis crosstalk can help to elucidate these respiratory and digestive system interactions (Figure 5). Dysbiosis occurs when there are detrimental changes in the microbial composition of the gut or respiratory tract. It often leads to altered immune responses and the development of diseases, such as COVID-19. Nonetheless, of gut dysbiosis can be manipulated for treatment purposes[32,67-69]. Studies suggest that SARS-CoV-2 from the lungs travels to the gut *via* the lymphatic system leading to disrupted gut permeability[70,71]. Furthermore, the extent of dysbiosis is associated with COVID-19 severity[4,72]. Therefore, understanding the crosstalk between the microbiome and the gut-lung axis during COVID-19 infection may provide therapeutic approaches.

GUT-BRAIN-LUNG AXIS CROSSTALK DURING COVID-19 INFECTION

Like the gut-lung axis, crosstalk between the microbiome and the gut-brain axis has been recognized and remains the topic[73-75]. Several studies have illustrated the role of the microbiome-gut-brain axis in different neurological disorders[76,77].

The interaction between the brain and the gut (also called the gut-brain axis) is bidirectional, with several pathways involved, including bacterial metabolites, neuroanatomical communications, neurotransmitters, and hormones[78]. The vagus nerve is primarily involved in such communication, and these molecules (neurotransmitters/hormones) are produced in the GI tract. During communication between neurotransmitters and hormones, they might interact with the receptors on the vagus nerve, relaying information to the brain[78-81]. Many hormones can cross the BBB and affect the CNS directly. Additionally, neuroendocrine pathways which operate *via* the hypothalamic-pituitary-adrenal (HPA) axis associated with stress

also affect the BBB. The stress-HPA axis is associated with the release of glucocorticoids such as cortisol from the adrenal cortex. Cortisol, is associated with augmented intestinal permeability and GI motility, affecting the gut microbiota[78,82-84]. The stress-HPA axis may also lead to inflammation and bacteria-derived impaired metabolite production, especially SCFAs[78,84]. Therefore, a thorough understanding of the gut-brain axis can help the development of therapeutic approaches *via* modulation of the gut microbial composition.

The gut microbiota might play a distinct role in controlling the host immune system, and research is underway to uncover more in this field[85,86]. The involvement of the lungs (gut-brain-lung axis) occurs when inflammation and neurodegeneration in the brain stem due to COVID-19 prevent cranial nerve signaling, disruptinganti-inflammatory pathways and normal respiratory and GI functions. Recently, the lungs have been associated in the crosstalk among the microbiota-gut-brain axis components, and this axis was also noted during COVID-19 (Figure 6)[34,78]. Moreover, in COVID-19 patients, alterations in the gut microbiota have been shown to reduce live microbes (Bifidobacterium and Lactobacillus) during intestinal microbial dysbiosis[87].

The microbial translocation to the gut and its subsequent damage may play a vital role in inferior clinical outcomes for the disease. The gut-brain-lung axis during COVID-19 infection can also offer clues indicate viable directions for therapeutic development[34].

HYPOXIA IN COVID-19 AND GUT MICROBIOTA

Abnormal cytokine release (cytokine storms) and inflammatory responses may be associated with hypoxia during severe COVID-19. Viral replication in the lungs leads to a cytokine storm, destroying normal lung function and causing hypoxemia, *i.e.*, low oxygen levels in the blood. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that regulates cellular functions such as cell proliferation and angiogenesis. In hypoxic conditions, HIF-1α binds to the hypoxemic response element and induces the production of cytokines such as IL-6 and TNF-α, leading to hypoxia[88]. There are other collective causes of hypoxia, including pulmonary

infiltration and thrombosis. The COVID-19 virus induces pneumonia that causes atelectasis (collapsing of air sacs), leading to low oxygen levels in the body[89]. Additionally, COVID-19 leads to mitochondrial damage, production of reactive oxygen species production and subsequently HIF-1α, further promoting viral infections and inflammation[90].

As part of its normal metabolic functions, the gut microbiota produces neurotropic metabolites, neurotransmitters, peptides, and SCFA, whose levels are disrupted due to COVID-19. SCFA such as butyrate confer neuroprotection. Modulation of gut microbes (responsible for such metabolite production) by SARS-CoV-2 alters hypoxia-sensing, negatively impacting the CNS[91]. Therefore, an association between gut microbiota and hypoxia in COVID-19 patients can be speculated, and may be linked to the CNS (Figure 7).

ALTERATION OF GUT MICROBIOTA IN COVID-19: EVIDENCE FOR INFLAMMATION OR DIEASE, SEVERITY?

Under normal conditions, colonization of the normal microbiota in the gut causes resistance to pathogen[92,93]. Much of the normal gut microbiota belongs to Clostridia., which produces butyric acid. This SCFA is produced during dietary fiber fermentation along with acetic acid and propionic acid, which play a critical role in gut health (Figure 8a)[94,95]. Butyric acid helps in maintain the integrity of the gut barrier by providing a vital energy resource for colonocytes. This SCFA also hinders histone deacetylase activity and inhibits the activation of the nuclear factor (NF)-κB signaling pathway activation. This phenomenon may activate the G protein-coupled receptor pair (GPR41 /GPR43). These events help exert an anti-inflammatory response in normal gut health and stimulate regulatory T cells (Treg cells)[96-100]. Treg cells play a central role in suppressing inflammatory responses[97,101]. However, in COVID-19 patients, typical microbiota dysbiosis causes an imbalance in all these events.

There is a distinct connection between dysbiosis of the gut microbiota and hyper-inflammatory responses, especially cytokine release, in some COVID-19 patients[102] (Figure 8). Researchers noted that gut microbiota composition is related to the

COVID-19 severity of and observed an association between altered cytokine levels and gut microbiota composition[38]. Cytokines/inflammatory factors, such as IL-1β, IL-6, and TNF-α, are usually associated with inflammation during disease[103]. In the case of severe COVID-19, the levels of certain cytokines, such as IL-6, IL-10, TNF-α, and IFN-are raised abnormally, and in some cases, cytokine storms are observed (Figure 8b)[23]. In pilot study, the quality of gut microbial composition was associated with the severity COVID-19 in 15 patients at the time of hospitalization in Hong Kong. The study showed an abundance of microbes such as *Clostridium hathewayi, Clostridium ramosum,* and Coprobacillus in COVID-19 patients. Moreover, an anti-inflammatory bacteria, *Faecalibacterium prausnitzii*, was be inversely correlated with disease severity[49].

Nonetheless, more detailed studies are needed to understand the impaired gut health during COVID-19, especially in extreme forms of the disease. Another study confirmed microbiota dysbiosis in COVID-19 patients. This study found differential bacterial populations with a decrease in *F. prausnitzii* and *Clostridium* spp and an association of IL-21 in mild to severe COVID-19 patients[51].

A gut microbiota richness analysis in COVID-19 patients was conducted over through a six-months evaluation using 16S rDNA sequencing. This study showed that, patients with decreased post-convalescence richness in bacterial microbiota had high disease severity with increased CRP. Additionally, the authors observed increased incidence of intensive care unit admissions with worse pulmonary functions in these patients[104]. The study suggested an association between the hyper-inflammatory response in COVID-19 and gut dysbiosis. However, a greater number of studies testing patients well after recovery are required to fully illustrate gut dysbiosis, associated factors, and the hyper-inflammatory response during COVID-19.

GUT MICROBIOTA INELDERLY OR CO-MORBID COVID-19 PATIENTS

Researchers have attempted to understand the role of the gut microbiota in elderly or co-morbid COVID-19 patients. A recent study evaluated the association of the gut microbiota and its modulation in COVID-19 patients. In this study, the cohort

comprised approximately 200 severe COVID-19 patients hospitalized with pneumonia. Researchers considered elderly patients (age 62 years to 64 years) and their comorbidity. Patients in this study received two types of treatments: one group was treated with only the best available therapy (BAT), and the other group was treated with oral bacteriotherapy and BAT. Researchers found a decline in mortality and decreased progress in severe disease. Finally, researchers concluded that oral bacteriotherapy might be helpful in the management of hospitalized COVID-19 patients[105]. Similarly, Rao *et al*[106] noted that people with the comorbiditiesare more prone to COVID-19-related complications. In this case, immune system deregulation and deaths were also noted. However, researchers used-glucan to enhance the immune system in COVID-19 patients. This glucan was used to augment the activity of macrophages, natural killercells, and IL-8, implicating that it might enhance the defense mechanisms to combat the virus[106].

Recently, Liu *et al*[1] evaluated the role of the gut microbiota composition and its association with the post-acute COVID-19 syndrome (PACS). In this study, researchers considered the comorbidities and dietary patterns during patient selection compare gut microbiota compositions. However, no considerable differences were observed in age, comorbidities, gender, antibiotics, or antiviral drug use between patients with PACS or without PACS[1].

Therefore, in cases of elderly or co-morbid COVID-19 patients, the gut microbiota might play an important role in immune system deregulation, although further studies are required to validate the findings.

GUT MICROBIOTA BASED ON ANTIBIOTIC USAGE IN COVID-19 PATIENTS

In COVID-19 patients, the use of antibiotics is relatively common. The frequently used antibiotics in COVID-19 patients are Azithromycin, Amoxicillin Clavulanate, Cephalosporin, Tetracycline[49,107], *etc*. The composition of the gut microbiota is hampered in COVID-19 patients due to the usage of antibiotics, occasionally causing antibiotic-associated diarrhea (AAD)[108]. Antibiotics usages in COVID-19 patients were increased the number of opportunistic pathogens compared with that detected

in an untreated control group. Zuo *et al*[49] reported that the gut of COVID-19 patients, using antibiotics contains opportunistic bacterial pathogens such as *Bacteroides nordii*, *Actinomyces viscosus*, and *Clostridium hathewayi*. Additional studies also reported this phenomenon[22,109]. An increase of opportunistic bacterial pathogens causes dysbiosis of the gut. Rafiqul Islam *et al* also noted that the abundance of opportunistic pathogens in COVID-19 patients in Bangladesh could cause dysbiosis, with 46 genera of opportunistic bacteria being identified patient GI samples[110]. However, a study demonstrated that particular strains of probiotics may be useful for AAD[111]. Scientists have shown that the administration of oral probiotics can recover gut health and have antiviral effects[112,53]. For probiotic strain identification, Mak *et al*[113] highlight the need for effective research to easily recognize the probiotic strains of therapeutic use. In this case, the probiotics should be specific for COVID-19, and help reduce the susceptibility to COVID-19 preventing severe COVID-19 disease.

GUT MICROBIOTA DYSBIOSIS DURING COVID-19 AND USE OF PROBIOTICS

Scientists identified an association between the gut microbiota dysbiosis and the severity of COVID-19. Magalhães *et al*[52] noted that gut microbiota dysbiosis causes poor outcomes in elderly COVID-19 patients with hypertension and diabetes. Additionally, co-morbid elderly COVID-19 patients were prone to increased inflammatory situations due to the dysbiosis. The elevated amount of bacterial products in the gut might translocate into the blood due to the increased permeability across the intestinal epithelium. Bacterial toxin products, such as LPS, may accumulate in blood, aggravating TLR4 and subsequent downstream signaling. This could contribute to the "cytokine storm", and result in complications in elderly COVID-19 patients[54]. Researchers also found a different route of activation of toll-like receptor (TLR)4/ TLR5 in COVID-19 patients[114-116]. Hung *et al*[53] also reported that gut microbiota dysbiosis increases COVID-19 severity in the elderly. However, the use of probiotics is a novel way to reduce COVID-19 severity in elderly populations.

THERAPEUTIC IMPLICATIONS AND CLINICAL TRIALS TO UNDERSTAND THE ROLE OF THE GUT MICROBIOTA DURING COVID-19

A careful analysis of the microbiome-gut-lung axis during COVID-19 infection can direct research towards therapeutic options for restoring gut health. As an altered gut microbiota is strongly associated with COVID-19 and its severity, supplementation of bacterial metabolites or commensals and prebiotics to enrich the microbial ecosystem is a path toward effective therapeutic options.

However, very few studies have explored this. A randomized clinical trial with 300 registered participants assessed the effectiveness of combination therapy using *Lactobacillus plantarum* (*L. plantarum*) CECT 7484, *L. plantarum* CECT 30292, *Pediococcus acidilactici* (*P. acidilactici*) CECT 7483, and *L. plantarum* CECT 7485, in adult COVID-19 patients (ClinicalTrials.gov; Clinical trial no. NCT04517422). Nonetheless, a deficiency of well-established data calls for more studies of this nature[41]. An open-label, randomized clinical trial with 350 participants conducted by Kaleido Biosciences sought to determine the effectiveness of a novel glycan molecule (KB109) in patients with mild to moderate COVID-19 (ClinicalTrials.gov; Clinical trial no. NCT04414124)[122]. The synthetic glycan molecule reduced the number of acute care visits by COVID-19 patients. Additionally, disease resolution in patients with comorbidities was improved, compared to that in patients relying solely on supportive self-care.

A similar study attempted to evaluate the glycan molecule's effectiveness (KB109) associated with gut microbiota function in COVID-19 patients. The same organization conducted the clinical study, an open-label, randomized clinical trial in 49 participants in the United States (ClinicalTrials.gov; Clinical trial no. NCT04486482)[117]. There were no conclusive results; however, more studies are likely to be conducted in this sense. A complete list of the clinical trials initiated to understand the role of the gut microbiota in COVID-19 and its therapeutic implications are shown in Table 4.

As the pandemic persists, it is critical to assess the effect of next-generation probiotics, prebiotics, synbiotics, and increased fiber intake on changes in gut microbiota composition in patients with mild to moderate and severe COVID-19.

FUTURE PERSPECTIVE

In several cases, complex pathophysiological and immunological responses are reported in the host due to SARS-CoV-2 infection. However, very little is known regarding the changes in gut virome in the COVID-19 patients, and this should be explored in future studies should explore it further. Moreover, the possible role of the gut microbiota in COVID-19 should be explored in future research. Likewise, population-based cohorts should be generated to illustrate the function of the altered gut microbiota during COVID-19 in different populations. This will enable the design of diagnostics and therapeutics for COVID-19 in different population types. Simultaneously, population-specific changes need to be described as this can help resolve severe conditions in COVID-19 patients. In the future, researchers should attempt to understand population-specific gut microbiota alteration during COVID-19 to design therapeutic interventions as required. Moreover, research could focus on the population specific changes in the immune response generated against the two altered gut microbiota during COVID-19.

CONCLUSION

Presently, abundant research has described the marked changes in the gut microbiomes of COVID-19 patients. Therefore, an apparent association exsists between the overall health of the gut microbiome and the progression of COVID-19[118]. Furthermore, the altered gut microbiota has been shown to persist in patients even after several days of recovery from COVID-19.

However, poor outcome were observed in elderly or co-morbid patients[97,119]. Recently, several studies discussed the factors associated with the modified gut microbiota in COVID-19 patients manifesting GI symptoms. According to some reports, increased inflammation may lead to a leaky gut, which enables the

translation of bacterial metabolites and toxins into the systemic circulation[97,120]. This might cause further complications to the severe COVID-19 patients.

In this review, we have illustrated various GI aspects of COVID-19 patients including the gut microbiota imbalance and GI symptoms, the patterns of altered gut microbiota composition, the crosstalk between the microbiome and the gut-lung axis, the crosstalk between the microbiome and the gut-brain-lung axis, as well as hypoxia associated with altered gut microbiota. We also highlighted the association between the gut microbiota and elderly or co-morbid COVID-19 patients, as well as that of gut microbiota dysbiosis and COVID-19 severity. Additionally, we explored the correlation between, probiotics usage and the gut microbiota based on antibiotic usage in COVID-19 patients. Therefore, our review will provide a distinct outline for researchers working in the field. Also, it will provide valuable insight into the role of gut microbiomes in COVID-19 patients.

Currently, therapeutics are in development to combat COVID-19. In addition to antiviral therapeutics, probiotics might be effective for improving gut health through the gut-lung axis. Recently, several clinical trials have been initiated to understand the role of probiotics in COVID-19 patients. The ongoing clinical trials will elucidate the role of probiotic therapeutics or for COVID-19 patients, and offer new alternatives in COVID-19 treatment.

Figure Legends

Figure 1 The schematic diagram shows normal healthy gut and the incidence in gut microbiota and gut virome in coronavirus disease 2019 patients. COVID-19: Coronavirus disease 2019.

Figure 2 The schematic diagram illustrates the syndrome coronavirus 2 entry in the body, causes of gut microbiota imbalance which assists in manifesting the gastrointestinal symptoms in coronavirus disease 2019 patients. GI: Gastrointestinal; SARS-CoV-2: Syndrome coronavirus 2.

Figure 3 The diagram illustrates increased or decreased gut microbiota in coronavirus disease 2019 patients, including bacterial, viral, and fungal populations. COVID-19: Coronavirus disease 2019.

Figure 4 The diagram illustrates different types of mapped gut microbiota in coronavirus disease 2019 patients. Pro-inflammatory microbiota, opportunistic microbiota, the microbiome in severe coronavirus disease 2019 (COVID-19) patients, and the microbiome in low to moderate COVID-19 patients, anti-inflammatory microbiota, and beneficial microbiota. COVID-19: Coronavirus disease 2019.

Figure 5 The diagram points out the normal gut and its microbial association. The figure also illustrates the crosstalk between the microbiome and gut-lung axis. SARS-CoV-2: Syndrome coronavirus 2.

Figure 6 The diagram describes the normal gut and its microbial association. The figure also illustrates the crosstalk between the microbiome and gut-brain-lung axis. BDNF: Brain-derived neurotrophic factor; HPA: Hypothalamic-pituitary-adrenal; SARS-CoV-2: Syndrome coronavirus 2.

Figure 7 The figure illustrates an association between gut microbiota and hypoxia in coronavirus disease 2019 patients, and it is connected with central nervous system. SARS-CoV-2: Syndrome coronavirus 2.

Figure 8 The figure illustrates normal gut microbiota and immunological consequences, and coronavirus disease 2019 related altered gut microbiota associated inflammation. A: Normal gut microbiota and immunological consequences for healthy gut; B: Coronavirus disease 2019 (COVID-19) related altered gut microbiota associated inflammation. The inflammatory condition in COVID-19 patients causes the abnormal release of different cytokines, such as interleukin-1 beta (IL-1β), IL-6, IL-8, IL-10, IL-12, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-alpha, and interferon-gamma. PSA:

Polysaccharide A; SCFA: Short-chain fatty acid; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; GMCSF: Granulocyte-macrophage colony-stimulating factor; TNF-α: Tumor necrosis factor-alpha; IFN-γ: Interferon-gamma.

Table 1 Different gastrointestinal symptoms in coronavirus disease 2019 patients

S. No.	Total number of human subjects involved in study	Demographics of the study populations	Vomiting	Diarrhea	Nausea	Remarks/study summary	Reference
1	191	Adults (46-67 years) hospitalised, Chinese peoples, 91 patients having comorbidity	7 (3.7%)	9 (4.7%)	7 (3.7%)	Identification of several risk factors and a detailed clinical course of illness for mortality of COVID-19 patients	[121]
2	171	Minor aged (1 d-15 years, hospitalised, Chinese children, no such comorbidity	11 (6.4%)	15 (8.8%)	NA	Report of a spectrum of illness from children infected with SARS-CoV-2 virus	[122]
3	1099	Median age group (35-58 years), hospitalised,	55 (5.0%)	42 (3.8%)	55 (5.0%)	Identification and definition of clinical characteristics	[37]

		Chinese patients without any comorbidity				and disease severity of hospitalized COVID-19 patients	
4	140	Adults (25-87 year), hospitalised Chinese patients with high comorbidity	7 (5.0%)	18 (12.9%)	24 (17.3%)	Report on hospitalized patients having COVID-19 with abnormal clinical manifestations (fever, fatigue, gastrointestinal symptoms, allergy)	[123]
5	73	Adults hospitalised Chinese patients, comorbidity reported	NA	26 (35.6%)	NA	Clinical significance of SARS-CoV-2 by examining viral RNA in feces of COVID-19 patients during hospitalizations	[124]
6	52	Adults (mean age 59.7 year), critically ill ICU admitted Chinese patients,	2 (3.8%)	NA	NA	Retrospective, single-centered, observational study on critically ill, ICU-admitted	[125]

		comorbidity reported				adult COVID-19 patients	
7	138	Adult (median age 56 years), hospitalised Chinese patients with comorbidities	5 (3.6%)	14 (10.1%)	14 (10.1%)	Clinical characteristics of COVID-19 patients in hospitalized conditions	[126]
8	41	Middle age group (41-58 years) hospitalised Chinese patients with comorbidities	NA	1 (2.6%)	NA	Epidemiological, laboratory, clinical, and radiological features and treatment with clinical outcomes of hospitalized COVID-19 patients	[46]
9	62	Studied patients (median age 41 years) were hospitalised, Chinese ethnicity and comorbidity reported	NA	3 (4.8%)	NA	Most common symptoms at onset of illness with clinical data in confirmed COVID-19 patients	[127]
10	137	Studied patients (mean age 57-	NA	11 (8%)	NA	Investigation of epidemiological history, clinical	[128]

		55) ware Chinese and hospitalised, comorbidity was also noted				characteristics, treatment, and prognosis of COVID-19 patients	
11	81	Chinese patients (mean age was 49.5 years), hospitalised with high comorbidities	4 (4.9%)	3 (3.7%)	NA	Report of confirmed COVID-19 patients with chest computer tomography imaging anomalies	[129]
12	99	Hospitalised, Chinese patients (average age of the patients was 55.5 years), comorbidity was reported	1 (1%)	2 (2.0%)	1 (1%)	Inclusive exploration of epidemiology and clinical features of COVID-19 patients	[130]

NA: Not available; ICU: Intensive care unit; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Syndrome coronavirus 2.

Table 2 Fecal viral shedding in coronavirus disease 2019 patients

S. No.	Total number of human subjects in study	Demographics of the study populations	Gastrointestinal symptoms	Confirmed cases of fecal shedding	Remarks/study summary	Reference
1	205	Patients (mean age of 44 years) were hospitalised, Chinese without any comorbidities	No symptoms	44	Evidence-based study for gastrointestinal infection of SARS-CoV-2 virus and its possible fecal-oral transmission route in humans	[133]
2	73	Different age group (10 mo to 78 years old), hospitalised Chinese patients without report any comorbidities	Gastrointestinal bleeding, diarrhea	39	Description of epidemiological and clinical characteristics of COVID-19 patients	[124]
3	10	Chinese patients have	Hemoptysis, diarrhea, cough	8	Report of median aged	[127]

		aged 19-40 years, hospitalised and no such comorbidity was reported			COVID-19 confirmed patients in ICU	
4	14	Patients (18-87 years) were hospitalized, Chinese individuals without any comorbidities	No symptoms	5	Retrospective analysis of laboratory-confirmed COVID-19 cases in hospitalized conditions	[132]
5	66	Chinese patients (median age of 44) were hospitalised, comorbidity was not reported	No symptoms	11	Viral RNA detection was performed from throat swabs, stool, urine, and serum samples in different clinical conditions in COVID-19 patients	[133]
6	18	Adults patients (median age, 47 years) from Singapore	No symptoms	4	COVID-19 patient case series using clinical, laboratory, and	[134]

37

		were hospitalised and comorbidities was noted			radiological data	
7	74	Studied paients belonged from China and were hospitalised with comorbidities	No symptoms	41	Analysis of respiratory and fecal samples to determine clinical symptoms and medical treatments of COVID-19 patients	[135]
8	9	Adults Chinese patients were hospitalised without any comorbidities	Diarrhea and urinary irritation	2	Detection of SARS-CoV-2 RNA in urine and blood samples, and anal, oropharyngeal swabs of confirmed COVID-19 patients	[136]

17

ICU: Intensive care unit; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Syndrome coronavirus 2.

Table 3 Analysis of gut microbiota in coronavirus disease 2019 patients in different cohorts

Sl. no	Cohort composition	No of Patients	Demographics of the study populations	Country	Significant gut microbiota found	Study conclusion	Reference
1	A pilot study with 15 healthy individuals (controls) and 15 patients with COVID-19	15	Study performed with hospitalised patients (median age 55), Chinese ethnicity and comorbidities were reported	Hong Kong	Abundance of *Clostridium hathewayi, Clostridium ramosum, Coprobacillus,* which are correlated with COVID-19 severity	Change in the fecal microbiome of COVID-19 patients during hospitalization, compared to healthy individuals (controls)	[48]
2	The two-hospitals cohort, serial stool samples collected from 27 COVID-19 patients among 100	27	Adults hospitalised Chinese patients, comorbidities were noted	Hong Kong	*Faecalibacterium prausnitzii, Eubacteriumrectale* and bifidobacteria	Gut microbiome involved in COVID-19 severity	[38]
3	United States cohort (majority African American)	50	Studied patients (mean age 62.3 years) were hospitalised with comorbidities, American	United States	Some of the significant genera (*Corynebacterium Peptoniphilus, Campylobacter, etc.*)	No significant associations found between the composition microbiome and disease severity from	[50]

No.	Study	N	Population	Country	Elevated microbes	Conclusion	Ref
			ethnicity			COVID-19 patient gut microbiota	
4	The study used 53 COVID-19 patients and 76 healthy individuals. 81 fecal samples collected during hospitalization	53	Adults Chinase hospitalised patients, no such comorbidities were noted	China	Elevated gut microbes such as *Rothia mucilaginosa*, *Granulicatella* spp, *etc.*	COVID-19 infection linked with change of the microbiome in COVID-19 patients	[137]
5	15 patients Cohort	15	Study performed adults hospitalised patients with comorbidities, Chinese ethnicity	Hong Kong	Elevated bacterial species *Collinsella tanakaei* ,*Collinsella aerofaciens*, *Morganella morganii*, *Streptococcus infantis*	The study found fecal viral (SARS-CoV-2) activity	[54]
6	Two-hospital cohort with a total of 100 patients. Stool samples collected from 27 patients	27	Hospitalised adults patients were from China, comorbidities were noted	Hong Kong	Several gut microbiota such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and bifidobacteria	Gut microbiota associated disease severity and inflammation in COVID-19 patients	[38]

7	98 COVID-19 patients (3 asymptomatic, 34 moderate, 53 mild, 3 critical, 5 severe), serial fecal samples collected from 37 COVID-19 patients	37	Adults (mean age 37) patients, hospitalised condition from Chinese ethnicity, comorbidities were reported	Hong Kong	A total of 10 virus species in fecal matter (9 DNA virus species and 1 RNA virus, pepper chlorotic spot virus)	Analysis of gut virome (RNA and DNA virome) in COVID-19 patients	[47]
8	Study of fecal samples from 30 COVID-19 patients	30	Patients (mean age 46) were hospitalised from Chinese groups, comorbidities were noted	Hong Kong	Increased proportions of fungal pathogens (*Candida albicans, Candida auris, Aspergillus flavus, Aspergillus niger*) in fecal samples	Analysis of fecal fungal microbiome of COVID-19 patients	[48]

COVID-19: Coronavirus disease 2019.

Table 4 List of clinical trials initiated to understand the role of gut microbiota in coronavirus disease 2019 and its therapeutic implications

Sl No.	Objective of clinical trials	Clinical trials No.	Description of clinical trials	Remarks
1	Evaluate the combination of probiotics (*P. acidilactici* and *L. plantarum*) to reduce the viral load of moderate or severe COVID-19 patients	NCT04517422	It was a randomized controlled trial, 300 participants, treatment by dietary supplement (probiotics)	Observational study of adult and older adult, trial completed
2	To explore the natural history of mild-to-moderate COVID-19 illness and safety of a novel glycan (KB109) and self-supportive care	NCT04414124	It was a randomized, prospective, open-label, parallel-group controlled clinical study of 350 participants	Observational study of adults (both male and female), trial completed
3	Investigate the physiologic effects of the novel glycan (KB109) on patients with COVID-19 illness on gut microbiota structure and function in the outpatient	NCT04486482	It was a randomized, open-label clinical study of 49 participants	Observational study of adults patients with mild-to-moderate COVID-19 infections, trial completed
4	Evaluate the clinical contribution of the gut microbiota and its	NCT05107245	It was case-control, diagnostic study of 143 participants	Observational study on the diagnostic

	diversity on the COVID-19 disease severity and the viral load			evaluation of the human intestinal microbiota, trial completed
5	Studied the effects of *Lactobacillus coryniformis* K8 intake on the prevalence and severity of COVID-19 in health professional	NCT04366180	A randomized, interventional study of 314 participants	Investigation of probiotic effects to healthcare personnel exposed to COVID-19 infection
6	Investigate to exploring the role of nutritional support by probiotics to COVID-19 outpatients (adult)	NCT04907877	Randomized, evidence based study of 300 participants	Used of probiotics as dietary supplement that enhance specific immune response of patients having COVID-19 respiratory infection
7	Use of dietary supplement (Omni-Biotic® 10 AAD) can decrease the intestinal inflammation and improves dysbiosis for COVID-19 patients	NCT04420676	It was a randomized Interventional study of 30 participants	This study performed as double blind, placebo-controlled study
8	Evaluate the probiotics efficacy to	NCT04621071	The double-blind, randomized,	This study performed to

	decrease the COVID-19 infection symptoms and duration of COVID-19 positive patients		controlled trial of 17 participants	explored the effects of dietary supplement: Probiotics (2 strains 10×10^9 UFC), trial completed
9	Impact analysis of probiotic strain *L. reuteri* DSM 17938 for specific Abs response against SARS-CoV-2 infection	NCT04734886	It was control, randomized trial of 161 participants	To assess the upon and after COVID-19 infection in healthy adults, trial completed
10	To evaluate the primary efficacy of live microbials (probiotics) for boosting up the immunity of SARS-CoV-2 infected persons (unvaccinated)	NCT04847349	It was double-blind, randomized, controlled trial of 54 participants	Efficacy analysis of dietary supplement (combination of live microbials) as anti COVID-19 infection, trial completed
11	Evaluate the follow - up of Symprove (probiotic) to COVID-19 positive patients	NCT04877704	The randomized clinical trial was performed with 60 patients	Observational study to supervision of hospitalized COVID-19 patients
12	Study was performed to evaluate the possible effect of a	NCT04390477	It was randomized case control, clinical trial of 41	Observational study of dietary supplement:

	probiotic mixtures in the improvement of COVID-19 infection symptoms		participants	Probiotic to COVID-19 patients
13	The probiotic (Omni-Biotic Pro Vi 5) use for investigate the side effect of post-COVID syndrome	NCT04813718	It was a randomized trial of 20 participants	It was a therapeutic target study of probiotic for treatment of acute COVID-19 and prevention of post COVID infections
14	To evaluate the effect of a probiotic strain on the occurrence and severity of COVID-19 in hospitalised elderly population	NCT04756466	Randomized control trial of 201 participants	It was observational study, probiotic sued for improve the immune response of elderly patients
15	This study assesses the beneficial effects of the nutritional supplementation (ABBC1) to individuals taken the COVID-10 vaccine	NCT04798677	It was a double-blinded, placebo-controlled, randomized clinical study of 90 participants	Used as knowing the microbiome modulating properties, observational study
16	To investigate the consequence of *Ligilactobacillus*	NCT04922918	Non-randomised study of 25 participants	Observational study of aged patients having

	salivarius MP101 to hospitalised elderly individuals		highly affected by COVID-19
17	Study was performed to explored the effect of the probiotic *Lactobacillus rhamnosus* GG	NCT04399252	It was a randomized double-blind, placebo-controlled trail of 182 participants	Observational study of individuals microbiome of household contacts exposed to COVID-19
18	Treatment approaches by probiotics to human gut microbiome and growing the anti-inflammatory response for COVID-19 infected patients	NCT04854941	It was a randomized controlled open-label study of 200 participants	The optimizing treatment approaches based observational study, trial completed
19	To evaluate the capability of the novel nutritional supplement (probiotics and other vitamins) to COVID-19 infected and hospitalised patients	NCT04666116	Randomized, single blind clinical trial of 96 participants	Used of dietary supplementation with probiotics aims to reduce the viral load
20	Using of probiotics for COVID 19 transmission reduction to health care professionals	NCT04462627	It was a non-randomized trial of 500 participants	Analysis and reduction of COVID-19 viral load to health care

professionals[20]

P. acidilactici: *Pediococcus acidilactici*; *L. plantarum*: *Lactobacillus plantarum*; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Syndrome coronavirus 2.

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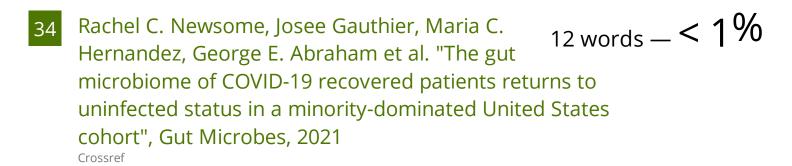Crossref

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