gastrointestinal disorders

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Review

The Effect of COVID-19 on Gut Microbiota: Exploring the Complex Interplay and Implications for Human Health

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Abstract: The COVID-19 pandemic caused by the SARS-CoV-2 virus has led to significant global health implications. Although the respiratory manifestations of COVID-19 are widely recognized, emerging evidence suggests that the disease may also significantly affect the gut microbiota, the intricate community of bacteria that lives within the gastrointestinal system. This extensive article intends to investigate the impact of COVID-19 on the gut microbiota, examining the underlying mechanisms, clinical implications, and potential therapeutic interventions. Understanding the complex interactions between COVID-19 and the gut microbiota will help us to gain valuable insights into the broader consequences of this viral infection on human health.

Keywords: COVID-19; gut microbiota; microbiome; dysbiosis

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Citation: Akter, S.; Tasnim, S.; Barua, R.; Choubey, M.; Arbee, S.; Mohib, M.M.; Minhaz, N.; Choudhury, A.; Sarker, P.; Mohiuddin, M.S. The Effect of COVID-19 on Gut Microbiota: Exploring the Complex Interplay and Implications for Human Health. *Gastrointest. Disord.* **2023**, *5*, 340–355. https://doi.org/10.3390/gidisord5030028

Academic Editor: Giuseppe Merra

Received: 19 June 2023
Revised: 6 August 2023
Accepted: 16 August 2023
Published: 18 August 2023

1. Introduction

The COVID-19 pandemic is a global health crisis caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a single-stranded enveloped positive-sense RNA virus with an average diameter of 75–150 nm that originated in Wuhan, China, at the end of 2019 and spread worldwide [1]. On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic [2], and to date, almost 7-million people have died from COVID-19 [3]. The virus predominantly affects the respiratory system, inducing a spectrum of symptoms that can range from mild-to-severe respiratory impairment, with several symptoms such as pyrexia, respiratory distress, pharyngitis, exhaustion, and myalgia [4]. In more severe cases, COVID-19 infection may lead to the development of pneumonia and acute respiratory distress syndrome (ARDS), which may require mechanical ventilation and lead to a significant risk of mortality [5].

In addition to respiratory manifestations, the pathogenesis of COVID-19 may result in systemic consequences such as the failure of multiple organs and physiological systems

throughout the body [6]. COVID-19 manifests as inflammation of the cardiac muscle (myocarditis) [7] and vascular organs (endotheliitis), which increases the risk of blood clots, leading to pulmonary embolism and deep vein thrombosis [8]. Several reports have suggested that COVID-19 is associated with arrhythmia [9] and myocardial infarction [10]. A group of neurological manifestations has been observed in patients with COVID-19, including loss of taste and smell [11], generalized headache [12], dizziness with vertigo [13], seizures [14], encephalitis [15], and Guillain–Barré syndrome [16]. However, the exact mechanism underlying these effects is still under the laboratory bench. Several digestive system symptoms, such as nausea, vomiting, diarrhea, and acute abdominal tenderness, have been observed in some COVID-19 patients [17]. Renal impairment with acute renal injury is found in COVID-19 patients as a result of an inflammatory reaction by the body or a direct viral invasion of the kidneys [18].

The human gastrointestinal tract (GIT) is densely populated by the microbiota. The gut microbiota, a collection of bacteria, viruses, and fungi that live in the gastrointestinal tract, not only maintains mucosal immunity but also regulates the host's systemic immune response [19]. Gut microbiota plays an important role in a broad range of physiological processes, from the digestion of complex polysaccharides to the regulation of neuronal signaling. In recent decades, it is getting more and more attention because of its association with a wide variety of diseases, ranging from metabolic disorders (e.g., diabetes and its complications) [20–25] to autoimmune diseases (such as rheumatoid arthritis, inflammatory bowel disease, and Type 1 diabetes), obesity [26], cancer [27], reproductive health [28–30], and sexual disorders [31,32], as well as neurodevelopmental disorders (e.g., autism) and neurodegenerative diseases (e.g., Alzheimer). Furthermore, modifying the microbiota in the human body may be a key factor for the treatment of disease. According to recent research on various respiratory disorders, gut microbiota may influence immunity and inflammation in the lungs [33]. Several studies observed an association between gut microbiota and SARS-CoV-2. In this review, we summarize the information that is currently available on the interaction between the gut microbiome and the host's immune response to SARS-CoV-2. We continue to explore the relevance of the diversity of the gut microbiome and the variations in its composition as diagnostic indicators, as well as the possibility of the gut microbiome as an interventional target in influencing COVID-19 results.

1.1. Understanding the Composition and Diversity of the Gut Microbiota

Around 100-trillion microorganisms (bacteria, fungi, viruses, protozoa, and viruses) are found in the human gut. The human genome is made up of 23,000 genes, while the microbiome encodes over 3-million genes that produce more than thousands of metabolites, impacting human health [34]. The composition and metabolism of the adult gut microbial communities are affected by a combination of factors, including diet, demographics, use of medication, health status, and environmental components shaping the gut environment [35–37]. Humans can be herbivorous, carnivorous, etc., depending on the culture, food supply, etc. The diversity of the distinctive microbes of each habitat varies considerably, even in healthy individuals, with a high specialization of niches within and between individuals. According to the Human Microbiome Project Consortium, the overall fecal microbiota richness was estimated to be 226 bacterial genera among 208 donors [38]. The microbiota of the human gut is dominated by two major phyla: Bacteroidetes and Firmicutes [39,40].

1.2. Factors Influencing Gut Microbiota Composition, Including Diet, Lifestyle, and Medications

The intestinal microbiota is integral to human halobionts. Past studies have shown that various factors, such as diet and drugs, play an important role in the composition and diversity of the intestinal microbiome [34,41,42]. Dietary patterns, as well as individual foods, can directly influence the diversity of the microbiome. Artificial sweeteners (sucralose, aspartame, saccharin) significantly increased Bacteroides, Clostridia, and other aerobic bacteria in the gut. Food additives like emulsifiers in processed food reduced

microbial diversity and increased inflammation promoting Proteobacteria [43,44]. Popular food-restrictive diets (vegan, raw food, gluten-free diets) can also impact gut microbial diversity. Some studies have shown the advantages of a vegan diet over an omnivorous diet, but others have not proven this theory [45]. Apart from food, drugs are also a key factor in the gut microbiota composition. Drugs such as proton pump inhibitors have a significant impact on microbial composition, which could explain the higher levels of gastrointestinal infection in people consuming these drugs. Antibiotics are impacting the intestinal microbiome [46]. Earlier observational human studies have shown an obesogenic effect in humans, even at low doses of antibiotics on food [47]. A Westernized lifestyle, such as behaviors, habits, and dietary patterns, may involve the alteration of gut microbiota. This lifestyle, which is characterized by a high intake of processed food, fructose corn syrup as an alternative of sugar, and unhealthy fats, was found to result in a higher prevalence of severe COVID-19 cases. Dietary habits can lead to underlying health conditions such as obesity, diabetes, and cardiovascular disorders, which are associated with the advancement of the diseases [48]. Several supplements such as Vitamin C, D, and zinc received attention due to their potential immune-boosting properties [49]. However, some studies suggested the effects of these supplements were inconclusive, and they are not proven cures or preventatives for COVID-19 [50].

1.3. Gut Microbiota Alterations in COVID-19 Patients

Several research investigations (Table 1) have explored alterations in gut microbiota in COVID-19 patients, illuminating the possible involvement of the gut microbiome in relation to the illness. The aforementioned investigation insights into the association between COVID-19 and gut microbiota dysbiosis, as well as its potential implications for the severity and treatment of the disease. A study conducted by Zuo et al. (2020) examined the gut microbiota composition in COVID-19 patients. The researchers observed a substantial reduction of beneficial commensal bacteria, such as Bifidobacterium and Lactobacillus, along with a corresponding increase in opportunistic pathogens, such as Clostridium hathewayi [51]. Another study conducted by Gu and colleagues in 2020 reported that the alteration of gut microbiota decreased the amount of butyrate-producing bacterial species, which are well-known for their potential anti-inflammatory effects.

Furthermore, investigations observed that patients with COVID-19 exhibit a reduction of microbial diversity. A study by Zuo et al. (2021) showed a reduction in the prevalence of bacterial species linked to elevated microbial diversity in COVID-19 cases, in comparison with subjects without any underlying health conditions. The connection between a decline in microbial diversity and higher vulnerability to inflammatory illnesses and infections implies that it may be involved in the development of COVID-19 [52]. Interestingly, modifications in the gut microbiota have also been correlated with the severity of COVID-19. According to Yeoh and colleagues' investigation conducted in 2021, it was identified that severe cases of COVID-19 were distinguished by a condition of gut dysbiosis, resulting in a decline in the presence of beneficial bacteria while allowing for an overgrowth of potential pathogens [53]. In another investigation conducted by Gu et al. in 2020, it was observed that patients with more severe symptoms have a discernible variation in the composition of their gut microbiota in relation to those experiencing milder symptoms [54]. These studies suggest a possible association between dysbiosis and the severity of symptoms associated with COVID-19.

Dysbiosis in the gut microbiota can lead to impaired regulation of the immune response, elevated systemic inflammation, and increased susceptibility to respiratory infections. Several studies have indicated that the dysbiosis of gut microbiota may play a role in the pro-inflammatory conditions witnessed in severe cases of COVID-19. Dhar and Mohanty (2021) reported that the alteration of pro-inflammatory cytokine levels observed in COVID-19 patients, accompanied by the evidence of gut dysbiosis, suggests a potential mechanism by which the gut microbiota influences the variability in disease outcomes [55].

The gut microbiota has recently been identified as a promising diagnostic and prognostic indicator for COVID-19. Researchers have identified specific microbial indicators that enable differentiation between individuals afflicted with COVID-19 from healthy individuals. Qin Liu and colleagues developed a diagnostic model based on gut microbiota demonstrating high efficacy in discerning patients with COVID-19 from those without the infection. Moreover, specific microbial profiles have demonstrated a correlation with the severity of diseases, proposing that gut microbiota analysis could serve as a promising prognostic tool [56].

It is important to consider that the treatment of COVID-19 has a significant effect on gut microbiota. The administration of antibiotics and antiviral agents has been reported to potentially disturb microbial equilibrium, which may ultimately worsen dysbiosis. A study by Lucie et al. reported in 2022 that COVID-19 patients receiving antibiotics had greater dysbiosis compared to those not receiving antibiotics, suggesting the need for prudent administration of antimicrobial agents to ameliorate the potential adverse effects on the gut microbiota [57]. Yeoh and colleagues observed correlations between specific gut microbial taxa and inflammatory markers such as C-reactive protein (CRP) and cytokines with pro-inflammatory properties [53].

Research investigating gut microbiota alterations in COVID-19 patients has elucidated the phenomenon of dysbiosis, a decline in microbial diversity, and potential associations with the severity of the illness. The role of gut microbiota in modulating the immune response and impact of systemic inflammation emphasizes its significance in the pathogenesis of COVID-19.

Table 1. Recent studies regarding the effect of COVID-19 on gut microbiota.

Study Group	Research Design	Population	Findings
Yeoh et al. [53]	Two centers prospective cohort study	100 COVID-19 patients vs. healthy individuals	- COVID-19 patients experience notable changes in their GI microbiota, characterized by dysbiosis. - Even after 30 days post-illness, dysbiosis continued to persist. - There is a significant correlation between dysbiosis and the severity of COVID-19 illness, as well as various serum pro-inflammatory markers.
Lv et al. [58]	Single center cohort study	56 hospitalized COVID-19 patients with sex-matched healthy subjects.	- Distinct variations in the metabolomes of COVID-19 patients were observed in comparison to those of healthy controls.
Gu et al. [54]	Single center prospective study	30 COVID-19 patients compared against 24 H1N1 patients	- COVID-19 leads to reduced bacterial diversity (dysbiosis), increased opportunistic pathogens, and decreased beneficial symbionts.
Zuo et al. [51]	Single center prospective study	15 COVID-19 patients compared against 15 healthy individuals	- COVID-19 patients exhibit significant dysbiosis in their GI microbiota.
Cao J et al. [59]	Cohort single center	108 COVID-19 patients, 22 patients with post COVID-19, 20 symptomatic pneumonia controls	- COVID-19 infections affect the microbiome, potentially influencing disease severity and recovery.
Reinold et al. [60]	Single center prospective study	54 COVID-19 patients received antibiotics; 40 patients received immunosuppression; over 15 patients were provided specific SARS-CoV treatment	- COVID-19 illness shows significant change in gut microbiotome
Nagata et al. [61]	Single center prospective study	112 hospitalized patients with SARS-CoV-2 infection and 112 non-COVID-19 control individuals	- COVID-19 directly involves in gut dysbiosis

1.4. Mechanisms of Gut Microbiota Dysbiosis in COVID-19

The complex and multifaceted causes of gut microbiota in COVID-19 are difficult to exclude. Although we are still improving our knowledge, several likely explanations have been suggested, according to existing research.

2. The Infiltration of Viruses and Disruption of the Intestinal Barrier

The infiltration of viruses and disruption of the intestinal barrier, SARS-CoV-2, the virus responsible for COVID-19, has been detected in the gastrointestinal tract, suggesting the possibility of direct viral invasion in the gut, suggesting the possibility of direct viral invasion within the gut. This invasion can disrupt the intestinal barrier by compromising its integrity, which results in increased gut permeability [62,63] As a result, deleterious microbial constituents and toxins possess the capacity to migrate across the bloodstream, eliciting an inflammatory reaction and dysbiosis [64].

2.1. Dysregulation of the Immune System

COVID-19 leads to cytokine storm, a hyperactive immune response characterized by the release of interferons, interleukins, tumor necrosis factors, chemokines, and several other mediators that causes injury to host cells (Figure 1). Systemic inflammation as a result of cytokine storm is very obvious [65]. These hyperinflammatory conditions disrupt the balance of the gut microbiota by eliminating both beneficial and harmful bacteria, which leads to dysbiosis. Gut microbial metabolite short-chain fatty acids (SCFAs), such as butyric acid and acetic acid, are pioneers for an immune response [66]. SCFAs can also act as inhibitors of histone deacetylase (HDAC), which results from a reduction of inflammatory responses by enhancing the amount and activity of T helper cells, regulatory T cells, and Th17 effector cells [67–70]. High Lipopolysaccharide (LPS) levels were observed in the circulation in severe and fatal lung injury cases [71]. The dysbiosis of gut microbiota facilitates the translocation of LPS into the portal circulation, which stimulates the hepatic kuffer cell to activate the NF–κB pathway and the secretion of TNF-α and IFN-β [51]. This can cause hepatic inflammation, as well as systemic inflammation [72].

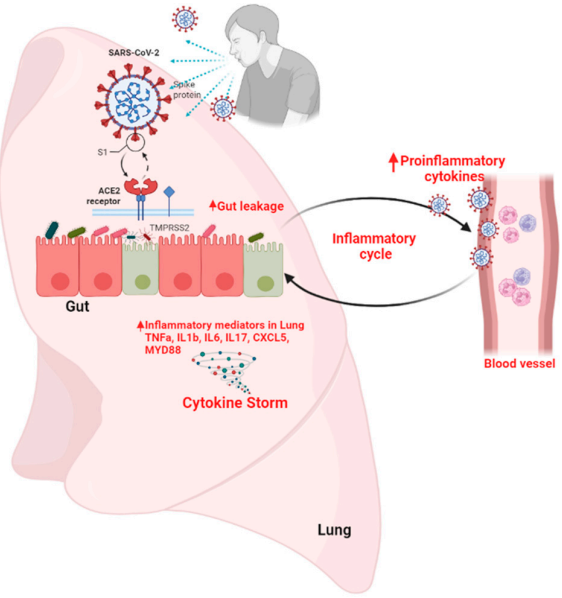

Figure 1. Possible mechanism of cytokine storm and subsequent pathogen infections resulting from lung microbiota dysbiosis in COVID-19 patients.

2.2. Effects of Antibiotic Treatments

A group of investigations previously conducted imply that the use of antibiotics can impact gut microbiota. Antibiotics such as amoxicillin [73], ciprofloxacin [74], and

cefprozil [75] have been found to have short and long time alterations of the taxonomic, genomic, and functional capacity of gut microbiota. The reduction of bacterial diversity has been observed by using broad-spectrum antibiotics [76] which causes the expanding and collapsing of the membership of specific indigenous taxa [77]. Antibiotics are widely used during COVID-19 management to reduce bacterial co-infections [78], which disrupts the gut microbiota by eliminating both beneficial and harmful microbiota [79]. This phenomenon has the potential to induce dysbiosis, which may further aggravate the vulnerability to secondary infections.

2.3. Dietary Modifications and Nutritional Alterations

Patients suffering from COVID-19 with severe symptoms experience altered dietary habits. These alterations, such as a reduced intake of dietary fibers, can impact the gut microbiome. Individuals consuming diets low in fiber tend to have reduced microbial diversity [80]. Several studies show dietary fiber replaced with animal protein and fat can alter microbial populations in the mortal gastrointestinal tract, as dietary fiber is the main source of energy for the microbiome [81–85].

2.4. Hospitalization and Stress

COVID-19 patients undergo several stressful events due to the new, unexperienced disease condition, such as isolation and hospitalization. Several studies show stressful events induced depression and anxiety, and they disrupted the gut microbiome. This gut dysbiosis persisted for at least 6 months [86].

3. Effects of Social Distancing and Quarantine

During COVID, social distancing and quarantining were prescribed, which led to changes in the types and amounts of food consumed. A shifting of the dietary habits impacts the gut microbiota composition and diversity [87]. Reducing the production of fresh food leads to an increased consumption of processed foods, which negatively affects gut health [88]. Social distancing and isolation can lead to increase stress, anxiety, and depression. These mental health stresses affect the gut–brain axis and, ultimately, gut microbiota alterations [89]. Quarantining may result in reduced physical activity levels, which influences gut microbiota diversity and metabolism [90].

3.1. The Gut–Lung Axis

A very interesting finding was observed in 1998, when Lyte and colleagues observed Anxiety-like behavior in rats after subclinical dosages of a single, unique bacterium (*Campylobacter jejuni*) were administered to them orally [91]. Later studies supported this finding, showing that mice exposed to C jejuni displayed anxiety-like behavior along with the activation of brain areas depending on signals ingested from the gut via the vagus nerve [92]. This is the first study to understand the gut–brain axis. However, a recent study discusses the gut–lung axis, which is a bidirectional communication pathway between the gastrointestinal tract (the gut) and the lungs. Despite being technically separate, the gut–lung axis (GLA) (Figure 2), along with possible anatomic interactions and intricate pathways involving their respective bacteria, has been proven to exist. Recent research has demonstrated the connection between dysbiosis and a number of lung-related conditions, including allergies, cystic fibrosis, asthma, and chronic obstructive pulmonary disease [93,94]. Due to the breakdown of the intestinal barrier as a result of dysbiotic circumstances, the inflammatory cascade in non-intestinal organs was mediated by the transfer of bacteria or microbial metabolites to the lungs [95,96]. In contrast to healthy people, the presence of the gut permeability marker fatty acid binding protein-2, as well as the gut microbial antigens peptidoglycan and lipopolysaccharides, was significantly higher in patients with COVID-19 [97].

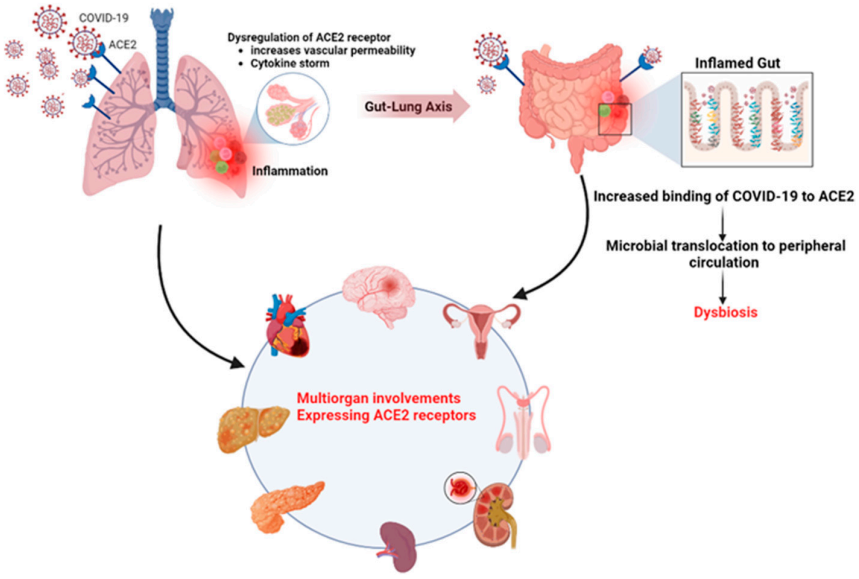

Figure 2. Schematic illustration of the involvement of the gut–lung axis in managing COVID-19 disease with dysbiosis of the gut microbiota. Since the gut–lung axis is bidirectional, lung inflammation affects the level of gut microbiota, while compounds originating from gut bacteria have an impact on the lung through blood.

3.2. The Role of the ACE2 Receptor in SARS-CoV-2 Infection and Gut Microbiota Dysbiosis

A homolog of Angiotensin-Converting Enzyme (ACE), called ACE2, has been reported as a negative regulator of the Renin–Angiotensin System (RAS), reducing the harmful effects caused by Ang II signaling through Ang II receptor Type 1 (AT1R) [98]. The ACE2 receptor plays a vital role in the infection process of the SARS-CoV-2 virus, which is responsible for COVID-19 [93]. ACE2 is present on the surface of numerous cells throughout the human body, including those in the digestive system, respiratory tract, lungs, heart, and kidneys [99].

SARS-CoV-2 enters host cells by interacting with ACE2 receptors on the cell surface. The virus's spike protein interacts with ACE2 to help the virus enter the cell. Once the virus has entered the host cell, it replicates and spreads, leading to COVID-19 symptoms. In the respiratory tract, the ACE2 receptor is highly expressed, which results from respiratory symptoms associated with COVID-19 [100].

ACE2 receptors are also highly expressed in the gut, particularly in the epithelial cells of the small intestine. Yifei and his colleagues found the presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. SARS-CoV2 RNA was detected in stool samples from 28 out of 42 (66.67%) laboratory-confirmed COVID-19 patients; this finding was unrelated to gastrointestinal symptoms or the severity of the illness [101]. Another study by Qun et al. observed SARS-CoV-2 had already replicated in the patient's rectum during the incubation period, with no obvious intestinal pathological damage. In this case, the patient developed a dry cough and fever in the early stage after the operation [102].

ACE2 plays a key role in controlling the effects of amino acid deficiency on microbial ecology and intestinal inflammation [103,104]. The gut microbiome of COVID-19 patients was significantly altered, with the opportunistic pathogen (such as *Clostridium hathewayi* and *Clostridium ramosum*) and an inverse correlation between probiotic bacteria (such as Lactobacillus and Bifidobacterium) and anti-inflammatory bacteria (such as *Faecalibacterium prausnitzii*) [52,105]. Furthermore, the immunological response elicited by the SARS-CoV-2 infection may contribute to intestinal dysbiosis [106].

SARS-CoV-2 infection-related dysbiosis may have systemic effects beyond the gut. Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are the most common. There is evidence that shows that intestinal microbial dysbiosis has a role in the pathogenesis of IBD [107]. Dysbiosis in systemic disease involves metabolic

disorders and metabolic diseases such as obesity or T2D [108], immune disorders [109], and mental health disorders [86].

3.3. Intestinal Inflammation and Gut Microbiota

Several gastrointestinal symptoms have been observed in a significant number of COVID-19 patients. A study by Tian et al. from March 2020 found that anorexia was the most often reported gastrointestinal symptoms in adults, occurring in between 39.9% and 50% of confirmed cases. Diarrhea was the second-most typical symptom, with it being reported in 2% to 49.5% of patients. In adults who tested positive for COVID-19, the prevalence of nausea and vomiting varied between 1% and 29.4%. The prevalence of abdominal pain in individuals with confirmed COVID-19 ranges from 2.2% to 6% in the literature [110]. The prevalence of abdominal pain among patients with confirmed COVID-19 ranges from 2.2% to 6%, which is less frequently described in the literature. In a study by Lei et al., among the 190 patients in our sample, 138 (69%) had at least one gastrointestinal symptom at the time of diagnosis; if hypoxia/anorexia were excluded, 93 patients (48.9%) had at least one gastrointestinal symptom. Diarrhea was one gastrointestinal symptom that was linked to a reduced mortality rate. Diarrhea was verified as an independent predictor of decreased mortality after multivariate analysis [111].

George Cholankeril and his group from Stanford University School of Medicine analyzed data collected from 116 patients who tested positive for the coronavirus at Stanford Health Care from 4–24 March 2020. 31.9% of the patients complained of gastrointestinal problems. The majority of those polled described their symptoms as minor. According to the study, 22% had a loss of appetite, 22% had nausea and vomiting, and 12% had diarrhea [112]. A group of researchers from New York Presbyterian Columbia University Medical Centre conducted a study on 147 patients. The most prevalent GI symptoms for COVID-19 in 147 patients without pre-existing GI conditions had diarrhea (23%), nausea/vomiting (21%), and abdominal pain (6.1%) at the time of hospitalization. At a median follow-up time of 106 days, the most prevalent GI symptoms were abdominal pain (7.5%), constipation (6.8%), diarrhea (4.1%), and vomiting (4.1%), with 16% reporting at least one GI symptom (95% confidence interval from 11 to 23%) [113].

3.4. Consequences of Intestinal Inflammation on Gut Barrier Function and Bacterial Translocation

The gut barrier, a selectively permeable structure, is widely recognized as an essential factor in the maintenance of intestinal homeostasis as it permits complex crosstalk between commensal intestinal microbes. Gut microbial dysbiosis due to both genetic and environmental factors can imbalance such equilibrium and may lead to intestinal inflammation, which ultimately triggers pathogenic microbe invasion and different pathogenic conditions such as inflammatory bowel diseases (IBD), Crohn's disease, irritable bowel syndrome, colorectal cancer, obesity, and Type-1 diabetes [35]. Inflammation can be triggered by components of the invading bacterium that can lead to a series of inflammatory pathways involving interleukins and other cytokines. In the same way, by-products of metabolic processes in bacteria, including some short-chain fatty acids, may play a role in inhibiting inflammatory processes. Persistently high levels of inflammatory mediators, such as lipopolysaccharides and interleukins, can initiate pathological processes that can lead to multiple chronic disorders [114–116].

3.5. Understanding the Interplay between the Gut Microbiota and the Immune System

There are two immune systems: the innate immune system and the adaptive immune system. The gut microbiota plays a crucial role in the development and maturation of the immune system, especially throughout childhood [117]. The immune system is trained to recognize and respond to pathogens while maintaining tolerance to harmless antigens through various mechanisms [118]. Microbial molecules and metabolites interact directly with immune cells to activate, proliferate, and differentiate. These interactions play a role in the regulation of immune responses and homeostasis [119]. The gut microbiota

helps to maintain the integrity of the intestinal barrier. Microbes help to improve the gut barrier by increasing mucus production and maintaining the structure of the intestinal epithelial cell layer. A good gut barrier stops harmful bacteria and toxins from entering your body, which can trigger your immune system [120]. Immune system dysfunction caused by COVID-19 may contribute to intestinal barrier dysfunction. The disruption of the intestinal barrier allows microbial components such as lipopolysaccharides (LPS) to escape from the gut into the bloodstream. This translocation induces an immune response and systemic inflammation, which can further affect the composition and function of the gut microbiota [114].

3.6. Impact on Short-Chain Fatty Acids (SCFAs)

Through the anaerobic fermentation of dietary fiber, the gut microbiota creates short-chain fatty acids (SCFAs). SCFAs, such as butyrate, propionate, and acetate, have important immunomodulatory effects and contribute to gut health [121]. SCFAs can affect the lung's immunological milieu and the severity of allergic inflammation [122]. The generation of SCFAs may be impacted by immunological dysregulation in COVID-19, altering immune responses and gut microbiota composition [123]. Fen Zhang and colleagues performed shotgun metagenomic sequencing on fecal samples from 66 antibiotics-naïve patients with COVID-19 and 70 non-COVID-19 controls. They observed impaired SCFA biosynthesis in the gut microbiome, which persisted beyond 30 days after recovery in patients with COVID-19 [124].

4. Long-Term Health Consequences of Gut Microbiota Alterations

Gut microbiota alterations, such as dysbiosis or imbalances in the composition and function of the gut microbial community, can have serious long-term health effects. Studies have revealed a connection between obesity and metabolic disorders like insulin resistance and Type 2 diabetes, as well as changes in the composition of the gut microbiota, such as a decline in microbial diversity [125,126]. Imbalances in gut bacteria can affect energy extraction from the diet, influence fat storage, and impact metabolic processes [127]. Inflammatory bowel illnesses, including Crohn's disease and ulcerative colitis, have been linked to imbalances in the gut microbiota that contribute to their onset and progression [128]. The progression of these disorders can be aided by disruptions in the delicate balance of gut bacteria, which can result in persistent inflammation of the intestinal lining [84,129]. An association between changes in the gut microbiota and the emergence of allergies and autoimmune illnesses is being supported by more research [130,131]. These disorders may be triggered or made worse by dysbiosis or an imbalance of gut bacteria, which may affect the immune system's regulation [132,133]. Emerging research indicates a potential link between gut microbiota and mental health issues such as anxiety and depression, as well as neurodevelopmental abnormalities such as autism spectrum disorders [134]. These relationships may be influenced by the gut–brain axis, a bidirectional communication link between the gut and central neurological system [135]. Some studies suggest that imbalances in gut microbiota composition may influence cardiovascular health by affecting lipid metabolism, blood pressure regulation, and systemic inflammation [136]. It has been shown that the gut microbiota changes as people age, and that changes in the gut's bacterial composition may be a factor in the development of age-related disorders like frailty, cognitive decline, and chronic inflammation [137]. However, the causal relationship and underlying mechanisms require further investigation.

Therapeutic Strategies and Interventions

Prebiotics and synbiotics on COVID-19-related gut dysbiosis is currently emerging. However, several therapies have been studied in the context of general gut health and immune support, which may have implications for COVID-19 and its impact on gut microbiota.

Probiotics have been explored for their immune-modulating properties and potential to support respiratory and gastrointestinal health. While there is limited direct data on their influence on COVID-19-related gut microbiota disease, probiotics could potentially help restore gut microbiota balance and improve gut health [138]. They play an important role to supporting immune response, reducing inflammation, and maintaining intestinal barrier integrity. However, further research is needed to establish their specific benefits in the context of COVID-19 [139].

Prebiotics, like the ones that have been mentioned above, provide nourishment to good gut microbes and encourage their growth. Prebiotics could be helpful by supporting the growth of beneficial bacteria and restoring gut microbiota balance, which is relevant to COVID-19-related gut dysbiosis. Prebiotics can contribute to a healthy gut barrier and immune function. Prebiotic-rich food such as fruits, vegetables, and whole grains are beneficial for overall gut health [140–143]. The Mediterranean diet has been demonstrated to have a positive effect on a healthy gut microbiome since it stresses whole, plant-based meals, healthy fats, and a moderate consumption of fish, poultry, and dairy while avoiding red meat and processed foods. The diet is rich in dietary fibers, which act as a probiotic and produce short-chain fatty acids (SCFAs). The Mediterranean diet also includes regular consumption of fatty fish, which provide omega-3 fatty acids. These omega-3 fatty acids act as an anti-inflammatory agent, which ultimately benefits gut microbiota. Several studies show that following a Mediterranean diet can enhance gut microbial diversity, which is regarded as a sign of a healthy gut microbiota [144–149].

Mesenchymal stem cell therapy [146] and fecal microbiota transplantation (FMT) is an approved therapy for recurrent clostridium difficile infection. The donor's stool shall be reconstituted from a range of solutions, including homogenization, filtering, or strain, and the following is administered after centrifugation either via the lower and upper GI tracts, or as gelatin capsules [147]. Bacteria (*Escherichia coli*, *Bifidobacterium*, *Lactobacilli*, and *Faecalibacterium prausnitzii*), viruses (*Anelloviruses*, *Microviridae*, and *Siphoviridae)*, archaea and fungus (*Candida albicans*), human colonocytes, and metabolites are among the fecal components that can be transported by FMT [148–150]. In order to prevent or cure CDI or IBD, FMT helps in the repair of an unbalanced gut microbiota.

5. Conclusions

The clinical effects of COVID-19 are catastrophic, and the GI tract's contribution is greatly underappreciated. Observational studies have shed light on the function of dysbiosis in acute and post-acute COVID-19 situations, as well as their connection to the severity of the illness. To uncover potential causal relationships between the human microbiome and COVID-19, a whole scenario investigation must be conducted. It is obvious that the microbiota has a significant role in how the host immune system reacts to different illnesses, including COVID-19. Finally, this study sheds new insight on COVID-19, emphasizing the critical role of gut microbiota and the importance of considering the gut–lung axis in the fight against this pandemic. We hope that our findings will spark more investigation and novel approaches to address COVID-19 and its systemic implications.

Author Contributions: Conceptualization, S.A. (Shamima Akter), S.T. and M.S.M.; methodology, M.C. and R.B.; software, M.C. and R.B.; validation, S.A. (Shahida Arbee) and M.M.M.; resources, N.M., A.C. and P.S.; writing—original draft preparation; writing—review and editing, M.C., R.B., S.A. (Shahida Arbee) and S.T.; visualization, M.C. and M.M.M.; supervision, M.S.M.; project administration, M.C. and M.S.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors want to acknowledge Svaksha Shukla, Jyothi, Arpita Barua, Amayah Mohiuddin, Vardaan Choubey, Lishant Tirumalasetty for their outstanding support.

Conflicts of Interest: The authors declare no conflict of interest.

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