Diagnostic, Prognostic, and Therapeutic Roles of Gut Microbiota in COVID-19: A Comprehensive Systematic Review

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Introduction: The Coronavirus Disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) emerged in late December 2019. Considering the important role of gut microbiota in maturation, regulation, and induction of the immune system and subsequent inflammatory processes, it seems that evaluating the composition of gut microbiota in COVID-19 patients compared with healthy individuals may have potential value as a diagnostic and/or prognostic biomarker for the disease. Also, therapeutic interventions affecting gut microbial flora may open new horizons in the treatment of COVID-19 patients and accelerating their recovery.

Methods: A systematic search was conducted for relevant studies published from December 2019 to December 2021 using PubMed/Medline, Embase, and Scopus. Articles containing the following keywords in titles or abstracts were selected: “SARS-CoV-2” or “COVID-19” or “Coronavirus Disease 19” and “gastrointestinal microbes” or “dysbiosis” or “gut microbiota” or “gut bacteria” or “gut microbes” or “gastrointestinal microbiota”.

Results: Out of 1,668 studies, 22 articles fulfilled the inclusion criteria and a total of 1,255 confirmed COVID-19 patients were examined. All included studies showed a significant association between COVID-19 and gut microbiota dysbiosis. The most alteration in bacterial composition of COVID-19 patients was depletion in genera Ruminococcus, Alistipes, Eubacterium, Bifidobacterium, Faecalibacterium, Roseburia, Fusicatenibacter, and Blautia and enrichment of Eggerthella, Bacteroides, Actinomyces, Clostridium, Streptococcus, Rothia, and Collinsella. Also, some gut microbiome alterations were associated with COVID-19 severity and poor prognosis including the increment of Bacteroides, Parabacteroides, Clostridium, Bifidobacterium, Ruminococcus, Campylobacter, Rothia, Corynebacterium, Megasphaera, Enterococcus, and...
INTRODUCTION

A pandemic caused by Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) emerged in late December 2019 (Zhu et al., 2020). The World Health Organization (WHO) named the consequent disease as Coronavirus Disease 2019 (COVID-19) and declared it as a global emergency due to the serious public health effects (Jamshidi et al., 2021). According to the report of the WHO, until February 1, 2022, there have been about 376 million confirmed cases and about 5.6 million deaths due to COVID-19 around the world.

The angiotensin-converting enzyme 2 (ACE2) receptor is a known SARS-CoV-2 receptor for entering host cells (Li et al., 2003; Zhou et al., 2020). This receptor is detected in various cells of the body such as the respiratory, digestive, renal, and skin epithelium, suggesting that each of these organs could be a potential target for the virus (Jamshidi et al., 2021; Xue et al., 2021). Moreover, virus RNA and viral particles have been identified in the fecal sample of COVID-19 patients, which may indicate the possibility of virus replication and activity in the human intestine (Gu et al., 2020a; Lamers et al., 2020; Xu et al., 2020).

Gut microbiota plays a well-known role in regulating immune system responses (Donaldson et al., 2016; Schirmer et al., 2016). Recent studies indicate the role of gut dysbiosis in the pathogenesis of various diseases such as inflammatory bowel disease, type 1 and type 2 diabetes, and celiac disease, as well as chronic respiratory diseases such as asthma, COPD, and cystic fibrosis (Jamshidi et al., 2019; Enaud et al., 2020).

Bacteria in the human intestinal flora appear to affect the respiratory system and lungs (especially the lung microbiota) by producing metabolites, endotoxins, cytokines, and intestinal hormones reaching the bloodstream, which is called the gut-lung axis (Budden et al., 2017; Dang and Marsland, 2019; Zhang et al., 2020).

On the other hand, there is evidence of the role of gut dysbiosis in the severity and prognosis of bacterial (e.g., *Streptococcus pneumonia*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*) and viral (e.g., H1N1 influenza) respiratory infectious diseases in animal models (Ichinohe et al., 2011; Fagundes et al., 2012; Fox et al., 2012; Brown et al., 2017). The use of broad-spectrum antibiotics that target the gut microbiota has led to a poor prognosis in mouse models with infectious lung diseases (Enaud et al., 2020).

Considering the important role of gut microbiota in maturation, regulation, and induction of the immune system and subsequent inflammatory processes, it seems that evaluating the composition of gut microbiota in COVID-19 patients compared with healthy individuals may have potential value as a diagnostic and/or prognostic biomarker of the disease. Also, therapeutic interventions affecting gut microbial flora may open new horizons in the treatment of COVID-19 patients and accelerating their recovery.

Keywords: COVID-19, SARS-CoV-2, gastrointestinal microbiome, dysbiosis, prognosis, diagnosis, gut microbiota, therapeutic

METHODS

This review conforms to the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement (Moher et al., 2009).

Search Strategy and Selection Criteria

To investigate the diagnostic, prognostic, and therapeutic role of the gut microbiota composition in COVID-19, a systematic search was conducted for relevant studies published from December 2019 to December 2021 using Pubmed/Medline, Embase, and Scopus.

Articles containing the following keywords in titles or abstracts were selected: "SARS-CoV-2" or “COVID-19” or “Coronavirus Disease 19” and “gastrointestinal microbes” or “dysbiosis” or “gut microbiota” or “gut bacteria” or “gut microbes” or “gastrointestinal microbiota”. Only studies included if they contained data about the gut microbiota composition in COVID-19 patients. There were no language restrictions. Review articles, duplicate publications, letters, commentary, animal studies, and articles with no relevant data were excluded from the analysis. Two authors (MA and FV) independently screened the articles by title and abstract. Full-text screening was conducted by two other authors independently (AT and YF). In each step, contrarieties were discussed with a third reviewer (PJ).

Data Extraction

A data extraction form designed by two authors (PJ and MJN) and, finally, selected data were extracted from the full text of eligible publications by PJ, YF, AT, MA, and FV. The following data were extracted for further analysis: first author’s name, year of
publication, country where the study was executed, type of study, study population, mean age, gender, COVID-19 severity of the cases, comorbidity(ies), microbiota analysis technique, intestinal microbiota alterations, biochemical and immunological alterations, and studied value of gut microbiota alterations in COVID-19. The data were jointly reconciled, and disagreements were discussed and resolved by review authors (PJ, MJN).

Quality Assessment
The critical appraisal checklist for case reports provided by the Joanna Briggs Institute (JBI) was used to perform a quality assessment of the studies (Institute, 2021).

RESULTS
As shown in Figure 1, the primary search resulted in 1,668 relevant articles, of which 47 articles were selected after title and abstract screening. Following the full-text screening, 22 articles fulfilled the inclusion criteria. Most of the studies were case-control (n = 9) followed by cohort (n = 9), clinical trial (n = 2), and cross-sectional (n = 2) studies. Fifteen of the studies were executed in China, 2 in Italy and 1 in UK, Portugal, India, Egypt, and Korea (Table 1).

A total of 1,255 confirmed COVID-19 patients were examined in 22 included articles (Table 1). Among the COVID-19 patients whose comorbidity was mentioned by the authors, the most common ones were hypertension (32.8%) and diabetes mellitus (17.8%). Other reported comorbidities were chronic respiratory disease (6.9%), cardiovascular disease (3%), immunosuppression (2.9%), dyslipidemia (2.3%), thrombotic events (2%), and renal impairment (1.6%). See Table 2.

Ten studies assessed gut microbiota composition alteration by fecal samples; one study used plasma samples, and it was not mentioned by the rest. The most commonly used techniques in these studies for detection and assessment of gut microbiota were 16s rRNA sequencing and shotgun metagenomic sequencing analysis (Table 1).

Gut Microbiome Dysbiosis of COVID-19 Patients
All included studies showed a significant association between COVID-19 and gut microbiota dysbiosis (Table 3). The most alteration in the bacterial composition of COVID-19 patients was depletion in genera Ruminococcus, Alistipes, Eubacterium, Bifidobacterium, Faecalibacterium, Roseburia, Fusicathenibacter, and Blautia and enrichment of Eggerthella, Bacteroides, Actinomyces, Clostridium, Streptococcus, Rotia, and Collinsella. Details are shown in Table 4.
TABLE 1 | Characteristics of the included studies.

| Authors                  | Year | Country | Type of study | Study population | Gut microbiota analysis technique       |
|--------------------------|------|---------|---------------|------------------|----------------------------------------|
| Gu et al. (2020b)        | 2020 | China   | Cross-sectional | 30 COVID-19, 24 H1N1, 30 HC | 16S rRNA sequencing                      |
| d’Ettorre et al. (2020)  | 2020 | Italy   | Clinical trial | 70 COVID-19 (case: 28, control: 42) | NM                                      |
| Tang et al. (2020)       | 2020 | China   | Cohort         | 57 COVID-19 (20 non-severe, 19 severe, 18 critical) | q-PCR                                   |
| Zuo et al. (2020a)       | 2020 | China   | Case-control   | 30 cases (COVID-19, 39 control) | Shotgun metagenomic sequencing          |
| Zuo et al. (2020b)       | 2020 | China   | Case-control   | 15 cases (COVID-19), 21 control (15 HC and 6 CAP) | Shotgun metagenomic sequencing and RT-PCR |
| Zuo et al. (2021a)       | 2020 | China   | Cohort         | 15 COVID-19 | Shotgun metagenomic sequencing          |
| Cao et al. (2021)        | 2021 | China   | Cohort         | 13 COVID-19, 5 HC | cDNA sequencing, bacteriome sequencing, metagenomic sequencing |
| Liu et al. (2021)        | 2021 | China   | Clinical trial | 11 COVID-19 | 16S rRNA sequencing                     |
| Lv et al. (2021b)        | 2021 | China   | Cohort         | 67 COVID-19, 35 H1N1, 48 HC | q-PCR on DNA extract of fecal samples |
| Lv et al. (2021a)        | 2021 | China   | Cohort         | 56 COVID-19, 47 HC | NM                                     |
| Yeoh et al. (2021)       | 2021 | China   | Cohort         | 100 COVID-19, 78 non-COVID-19 | Shotgun sequencing of DNA extracted from stools |
| Prasad et al. (2021)     | 2021 | UK      | Cohort         | 30 COVID-19, 16 HC | 16S rRNA sequencing, metatranscriptomic analysis (plasma samples) |
| He et al. (2021)         | 2021 | China   | Case-control   | 13 cases (COVID-19), 21 control (HC) | Metaproteomics |
| Zhou et al. (2021)       | 2021 | China   | Case-control   | 15 cases (recovered COVID-19 patients), 14 control (HC) | 16S rRNA sequencing |
| Moreira-Rosário et al. (2021) | 2021 | Portugal | Cross-sectional | 115 COVID-19 (19 mild, 37 moderate, 58 severe) | 16S rRNA sequencing |
| Wu et al. (2021)         | 2021 | China   | Case-control   | 53 cases (COVID-19), 76 control (HC) | 16S rRNA sequencing |
| Gabani et al. (2021)     | 2021 | Italy   | Case-control   | STUdy1: 69 COVID-19, 69 HC | 16S rRNA sequencing |
|                         |     |         |               | STUdy2: 69 COVID-19, 16 non-COVID-19 ICU admitted control |                                         |
| Kim et al. (2021)        | 2021 | Korea   | Case-control   | 12 cases (COVID-19), 36 control (HC) | 16S rRNA sequencing |
| Zuo et al. (2021b)       | 2021 | China   | Case-control   | 98 cases (COVID-19), 78 control (HC) | Shotgun metagenomic sequencing |
| Khan et al. (2021)       | 2021 | India   | Case-control   | 30 cases (COVID-19), 10 control(HC) | 16S rRNA sequencing |
| Hegazy et al. (2021)     | 2021 | Egypt   | Cohort         | 200 COVID-19 (122 mild, 78 moderate) | NM                                     |
| Wang et al. (2021b)      | 2021 | China   | Cohort         | 156 COVID-19 (98 mild and moderate, 58 severe and critical) | NM                                     |

*Healthy control subjects.
*42 patients received hydroxychloroquine, antibiotics, and tocilizumab, alone or in combination, and 28 patients received the same therapy added with oral bacteriotherapy, using a multistrain formulation.
*Community-acquired pneumonia.
*The efficacy of probiotic treatment has been studied only in 16 severe and critical COVID-19 patients (treatment group = 10, control group = 6).

Three articles surveyed the gut mycobiota alterations, and different results have been reported for different species of the same genus. About the Candida spp., an increase in Candida albicans and a decrease in Candida glabrata and Candida parapsilosis were mentioned. In regard to Aspergillus spp., enrichment of Aspergillus flavus and Aspergillus niger and a depletion of Aspergillus rugulosus, Aspergillus triticus, and Aspergillus penicilloides were reported. Also, one study indicated a reduction in seven unclassified species belonging to order Heliotiales, Pleosporales, and Sordariales, family Exidiaceae, and genera Microscypha and Emericellopsis in COVID-19 patients (Table 4).

According to all gut microbiota changes that were mentioned in the reviewed articles, a decrease in phyla Firmicutes and Bacteroidetes and an increase in phylum Actinobacteria among COVID-19 patients were inferred.

Association Between Gut Microbiota Composition and COVID-19 Severity

A few studies indicated the role of gut microbiome in COVID-19 severity (Table 4). In severe COVID-19 cases, Bacteroides spp., Parabacteroides spp., Clostridium spp., Bifidobacterium spp., Ruminococcus spp., Campylobacter spp., Rothia spp., Corynebacterium spp., Megasphaera spp., Enterococcus spp., and Aspergillus spp. were increased and Roseburia spp., Eubacterium spp., Lachnospira spp., Faecalibacterium spp., and Firmicutes/Bacteroidetes ratio were decreased significantly. In subjects with mild disease the observed significant change was in the enrichment of Eubacterium spp.

The alteration of the gut virome composition in severe COVID-19 cases was mentioned in two studies. In severe cases, fourteen Microviridae phages, one Inoviridae phage, one Podoviridae phage, and one unclassified virus were increased and...
plant-derived RNA virus, pepper chlorotic spot virus (PCSV), Myxococcus phage, Rheinheimera phage, Microcystis virus, Bacteroides phage, Murmansk poxvirus, Saudi mounouivirus, Sphaerotilus phage, Tomelloso virus, and Ruegeria phage were decreased significantly. See Table 4.

One study evaluated the associations between gut microbiota disturbance and SARS-CoV-2 viral loads and revealed that Prevotella copri and Eubacterium dolichicum were positively correlated and Streptococcus anginosus, Dialister spp., Alstipes spp., Ruminococcus spp., Clostridium citroniae, Bifidobacterium spp., Faecalibacterium spp., and Haemophilus parainfluenzae were negatively correlated with the viral load of SARS-CoV-2.

Biochemical and Immunologic Modifications in Relation to Gut Microbiota Alternations in COVID-19 Patients

In most studies, compared with healthy controls, COVID-19 patients had significantly higher levels of interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) and lower lymphocyte counts. According to one study, a positive correlation between Bifidobacterium spp. and prothrombin time (PT) and lactate dehydrogenase (LDH) was shown. Also, a negative correlation was reported between Atopobium spp. and D-dimer, Bacteroides spp. and LDH and creatine kinase (CK) level, Clostridium butyricum, and CRP and neutrophil count, and Faecalibacterium prausnitzii and CRP in critical COVID-19 patients. One study showed a specific relation between some genus of gut microbiota and immunological and biochemical modifications in critical and severe COVID-19 patients. In severe patients, Faecalibacterium prausnitzii and Clostridium leptum had a positive correlation with neutrophil count as well as Eubacterium rectale with IL-6 and Enterobacteriaceae with AST.

Another study indicated the specific relation of some species of gut microbiome and immune cells as the following: Bacteroides ovatus, Lachnospiraceae bacterium, and Eubacterium ventriosum had a positive correlation with CD4 and CD8 lymphocytes and other T-cells, in contrast to Bifidobacterium animalis and Escherichia spp. On the other hand, Faecalibacterium prausnitzii had a positive correlation with NK cells and Coprobacillus spp., Clostridium ramosum,
and *Clostridium symbiosum* had a negative correlation with them.

**Studied Value of Gut Microbiome in COVID-19**

All of the included studies showed a correlation between intestinal microbiota and COVID-19, and they studied the correlation in different aspects as in the following.

Four studies suggested that microbiota could have therapeutic properties with reducing gastrointestinal (GI) symptoms. *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* were the most common bacterial genera interventions used so far. Nine articles demonstrated intestinal microbiota modifications in infected cases with COVID-19 in which two of them confirmed the value of specified gut microbiota as a diagnostic tool and one of them studied gut microbiota changes during recovery time. Lachnospiraceae are a large family including *Fusobacterium*, *Eubacterium hallii* group, and *Roseburia*, and the Ruminococcaceae family including *Faecalibacterium prausnitzii* and *Ruminococcus* as well as *Clostridium* spp., *Bacteroides* spp., *Lactobacillus* spp., *Listeria* spp., *Actinomyces* spp., *Lactobacillus* spp., and *Streptococcus* spp. were the most common bacteria with diagnostic value. Thirteen studies demonstrated a relationship between gut microbiota changes and the intensity and prognosis of COVID-19. *Eubacterium*, *Faecalibacterium*, *Ruminococcus*, *Bacteroides*, *Clostridium*, *Lactobacillus*, *Bifidobacterium*, and *Roseburia* were the most notable bacterial genera with prognostic values. Details are shown in Table 3.

**DISCUSSION**

The interaction between gut microbiota and viral respiratory diseases such as COVID-19 is a complex, bilateral, and dynamic association. The current study emphasizes the role of the gut–lung axis (GLA) in the pathogenesis of COVID-19. One of the important aspects of GLA is the impact of gut microbiota on the supply and maintenance of the lung immune system, and its correlation with respiratory diseases and infections (He et al., 2017; Dang and Marsland, 2019; Ahmadi Badi et al., 2021; Allali et al., 2021). The gut and lung microbiome are closely related in health or disease conditions (Dickson and Huffnagle, 2015; Enaud et al., 2020; Ahmadi Badi et al., 2021). *SARS-CoV-2* may cause a dysbiosis in the lung microbiota to increase the population of inflammatory bacteria such as *Klebsiella oxytoca* and *Rothia mucilaginosa* which is associated with acute respiratory distress syndrome (Aktas and Aslim, 2020; Han et al., 2020; van der Lelie and Taghavi, 2020; Battaglini et al., 2021; Chattopadhyay and Shankar, 2021). The high levels of inflammatory cytokine productions during *SARS-CoV-2* invasion interfere with gut mucosal integrity and increasing risk of bacterial disposition to the bloodstream (Chattopadhyay and Shankar, 2021; Prasad et al., 2021).

Based on our findings, gut microbiota in patients with *SARS-CoV-2* is significantly affected, possibly due to systemic inflammatory response. Although the underlying mechanism for the observed dysbiosis is unclear, it might happen via downregulation of ACE2 expression that alleviates the intestinal absorption of tryptophan leading to decreased secretion of antimicrobial peptides and changes the composition of gut microbiota (He et al., 2020). In a healthy individual, intact bacteria and their fragments or metabolites such as des-amino-tyrosine and short-chain fatty acids (SCFAs) pass across the intestinal barrier via the mesenteric lymphatic system, reach the lung, and activate the innate immune system by the production of cytokines like type 1 interferon (IFN1) (Antunes et al., 2019). In the current study, *Faecalibacterium prausnitzii* and *Clostridium leptum* have a positive correlation with neutrophil counts in

**TABLE 3** Association between gut microbiota and COVID-19.

| Authors              | Type of study | Studied value | Association between gut microbiota and COVID-19 |
|----------------------|---------------|---------------|-----------------------------------------------|
| Gu et al. (2020b)    | Cross-sectional | Diagnostic   | Yes                                           |
| d’Ettorre et al. (2020)| Clinical trial | Therapeutic   | Yes                                           |
| Tang et al. (2020)   | Cohort        | Prognostic and diagnostic | Yes                                           |
| Zuo et al. (2020b)   | Case-control  | None          | Yes                                           |
| Zuo et al. (2020a)   | Case-control  | Prognostic and therapeutic | Yes                                           |
| Zuo et al. (2021a)   | Cohort        | Prognostic    | Yes                                           |
| Cao et al. (2021)    | Cohort        | Diagnostic and prognostic | Yes                                           |
| Liu et al. (2021)    | Clinical trial | Therapeutic (postinfection recovery) | Yes                                           |
| Lv et al. (2021b)    | Cohort        | Diagnostic    | Yes                                           |
| Lv et al. (2021a)    | Cohort        | Diagnostic and prognostic | Yes                                           |
| Yeoh et al. (2021)   | Cohort        | Prognostic    | Yes                                           |
| Prasad et al. (2021) | Cohort        | Diagnostic and prognostic | Yes                                           |
| He et al. (2021)     | Case-control  | None          | Yes                                           |
| Zhou et al. (2021)   | Case-control  | None          | Yes                                           |
| Moreira-Rosário et al. (2021) | Cross-sectional | Prognostic | Yes                                           |
| Wu et al. (2021)     | Case-control  | Diagnostic and prognostic | Yes                                           |
| Gaibani et al. (2021)| Case-control  | Prognostic    | Yes                                           |
| Kim et al. (2021)    | Case-control  | Diagnostic (postinfection recovery) | Yes                                           |
| Zuo et al. (2021b)   | Case-control  | Diagnostic and prognostic | Yes                                           |
| Khan et al. (2021)   | Case-control  | Prognostic    | Yes                                           |
| Hegazy et al. (2021) | Cohort        | Prognostic    | Yes                                           |
| Wang et al. (2021b)  | Cohort        | Therapeutic   | Yes                                           |
### TABLE 4 | Gut microbiota alterations.

| Authors | Intestinal microbial alternations |
|---------|-----------------------------------|
| Gu et al. (2020b) | **COVID-19 and H1N1 vs. HC**: Microbial diversity ↑, *Streptococcus spp.* ↑, *Escherichia-Shigella spp.* ↑ |
| **H1N1 vs. COVID-19 and HC**: | *phytum (Actinobacteria, Firmicutes)* ↑, *class (Actinobacteria, Erysipelotrichia, Clostridia)* ↑, *family (Lachnospiraceae)* ↑, *Blaurotus spp.* ↑, *Agathobacter spp.* ↑, *Anaerostipes spp.* ↑, *Fusificentibacter spp.* ↑, *Eubacterium hallii* ↑, *unclassified Lachnospiraceae* ↑, *Desulfovibrio spp.* ↑, *Bifidobacterium spp.* ↑, *Ruminococcus-2 spp.* ↑ |
| **COVID-19 vs. HC**: | *Ruminococcus gnavus* ↑ |
| Zuo et al. (2020b) | **Antibiotic positive COVID-19 group**: *Eubacterium hallii* ↑, *Bacteroides nordii* ↑ |
| **Antibiotic negative COVID-19 group**: | *Clostridium hathewayi* ↑, *Actinomyces viscosus* ↑, *Bacteroides vulgatus* ↑ |
| **Enriched in fecal samples in high infectivity**: | *Collinsella aerofaciens* ↑, *Morganella morganii* ↑, *Streptococcus infantis* ↑ |
| **Enriched in fecal samples in low to non infectivity**: | *Parabacteroides merdae* ↑, *Bacteroides stercoris* ↑, *Alistipes onderdonkii* ↑ |
| Lachnospiraceae bacterium↑ |
| **Virome**: | *Inoviridae*, *Mycoviridae*, *vorvidaridae* ↓ |
| **Antibiotic positive vs. antibiotic negative COVID-19 patients**: | *Bacteria*: *Subdoligranulum* ↑, *Roseburia inulinivorans* ↑, *Roseburia hominis* ↑, *Parasutterella excrementihominis* ↑, *Lachnospiraceae bacterium* 2_1_46FAA ↑, *Roseburia intestinalis* ↑, *Burkholderiales bacterium* 1_1_471 ↑, *Eubacterium hallii* ↑, *Parasutterella excrementihominis* ↑, *Alistipes indicus* ↑, *Coprobacter fastidiosus* ↑, *Eubacterium elgens* ↑, *Bacteroidiales bacterium ph8* ↑, *Bacteroides xylanivorans* ↑, *Odonobacter sphenunchus* ↑, *Alistipes shahii* ↑, *Ruminococcus bromii* ↑, *Bacteroides massiliensis* ↓ |
| **Virome**: | *No virus was identified as a different species.* |
| **Effect of disease severity on gut microbiome**: | *Viricella*: *Mucorales* ↓, *Escherichia-Shigella* ↓ |
| **Mild cases**: | *No viral community increased* |
| **Bacteria**: | *Sporolactobacterium durum* ↑, *Rothia mucilaginosum* ↑, *Enterococcus faecium* ↑, *Campylobacter gracilis* ↑, *Corynebacterium spp.* ↑, *Enterococcus spp.* ↑, *Rothia spp.* ↑, *Megasphaera spp.* ↑, *Campylobacter spp.* ↑, *Eubacterium hallii* ↑ |
| **Mild cases**: | *Eubacterium rectale* ↑ |
| Liu et al. (2021) | **After intervention (FMT)**: *Proteobacteria* ↑, *Actinobacteria* ↑, *Bifidobacterium spp.* ↑, *Faecalibacterium succinigenes* ↑, *Collinsella succinigenes* ↑ |
| Lv et al. (2021b) | **COVID-19 vs. others**: *Candida glabrata*, *Candida parapsilosis* ↑, Five unclassified species separately belonging to Helotes, Pleosporaales, Sordariales, *Microcystis spp.* ↓, *Erythrolobus spp.* ↓, *Cystobasidium spp.* ↓, *Prevotella copri* ↓ |
| Lv et al. (2021a) | **COVID-19 vs. others**: *Ruminococcaceae*, *Eubacteriaceae*, *Family XIII AD3011 group*, *Anaerostipes spp.* ↑, *Fusicientibacter spp.* ↑, *Roseburia spp.* ↑, *Faecalibacterium succinigenes* ↑, *Ruminococcus succinogenes* ↑, *Aspergillus niger* ↑, *Blautia spp.* ↑, *Clostridium ramosum* ↓ |
| Yeoh et al. (2021) | **Ruminococcus gnarus*** ↑, *Bacterdiais dorei* ↑, *Ruminococcus tongue* ↑, *Bacterodium vulgaris* ↑, *Bacterodium ovatus* ↑, *Bacterodium cacca* ↑, *Akermania muciniphila* ↑, *Bifidobacterium adolescentis* ↑, *Eubacterium rectale* ↑, *Ruminococcus bromit* ↑, *Subdoligranulum unclassified* ↑, *Bifidobacterium pseudocatenulatum* ↑, *Faecalibacterium prausnitzii* ↑, *Collinsella aerofaciens* ↑, *Ruminococcus obeum* ↑, *Bacterodium longicatena* ↑, *Caponosoccus* ↑, *Dorea formicigeners* ↓ |
| Prasad et al. (2021) | **Plasma samples**: *Pedomicrobium* ↑, *Acinetobacter* ↑, *Actinobacteria* ↑, *Alistipes onderdonkii* ↑, *Cupriavidus spp.* ↑, *Prevotella copri* ↑, *Aqualibacterium spp.* ↑, *Buklhiedera spp.* ↑, *Catabacteriia spp.* ↑, *Paraburkholderia spp.* ↑, *Bravibacterium spp.* ↑, *Sphingomonas spp.* ↑, *Staphylococcus spp.* ↑, *Lactobacillus spp.* ↑ |
| He et al. (2021) | **Ruminococcus gnarus** ↑, *Lachnospiraceae* ↑, *Tyzerella spp.* ↑, *Blaurotus spp.* ↑, *Eubacterium spp.* ↑, *Peptostreptococcaceae* ↑, *Butyri vibrio* ↑, *Ruminococcus spp.* ↑, *Lachnmobacteriaceae* ↑, *Bacteroides uniform* ↑, *Bacterodium garriolovus* ↑, *Bacterodium coprophili* ↑ |
| Zhou et al. (2021) | **Phylum (Actinobacteria)** ↑, *Family (Lachnospiraceae)* ↑, *Desulfovibrionaceae* ↑, *Faecalibacterium spp.* ↑, *Roseburia spp.* ↑, *Fusicientibacter spp.* ↑, *Ruminococcus spp.* ↑, *Clostridium XVIII*, *Dorea spp.* ↑, *Butyricoccus spp.* ↑, *Romboutsia spp.* ↑, *Intestinimonas spp.* ↑, *Bilophila spp.* ↑ |

(Continued)
TABLE 4 | Continued

| Authors | Intestinal microbial alterations |
|---------|---------------------------------|
| Moreira-Rosário et al. (2021) | **Severe cases**: Proteobacteria, Firmicutes/Bacteroidetes ratio↑, Roseburia spp↑, Lachnospira spp↓ |
| Wu et al. (2021) | **Blautia spp.**↑, **Ruminococcus bromii**↑, **Blautia obeum**↑, **Clostridium colinum**↑, **Clostridium citroniae**↑, **Bifidobacterium longum**↑, **Rotelia mucilaginosa**↑ |
| Gaibani et al. (2021) | **Escherichia spp.**↑, **Collinsella spp.**↑, **Streptococcus spp.**↑, **Weissella spp.**↑, **Enterococcus spp.**↑, **Rothia spp.**↑, **Lactobacillus spp.**↑, **Actinomyces spp.**↑, **Granulicatella spp.**↑, **Bacteroides caccae**↑, **Bacteroides coprophilus**↑, **Blautia obeum**↑, **Clostridium colinum**↑, **Blautia faecis**↑, **Butyricoccus pullicaeorum**↑, **Intestimomas butyricproducens**↓ |
| Kim et al. (2021) | **Eubacterium ventriosum**↑, **Citrobacter spp.**↑, **Shigella flexneri**↑, **Citrobacter freundii**↑, **Bacteroides thetaiotaomicron**↑, **Saccharomyces cerevisiae**↑, **E. coli**↑, **Staphylococcus aureus**↑, **Haemophilus influenzae**↑, **B. catenulatus**↑, **Bifidobacterium breve**↑, **B. longum**↑, **B. suis**↑, **B. adolescentis**↑, **B. distasonis**↑, **Butyricimonas spp.**↑, **Roseburia faecis**↓, **Roseburia inulinivorans**↓, **Roseburia faecis**↓, **Enterococcus spp.**↓, **Bacteroides phage**↓, **Flavonifractor spp.**↓, **Intestinibacter bartlettii**↓, **Flavonifractor plautii**↓, **Faecalibacterium prausnitzii**↓, **Roseburia inulinivorans**↓, **Fusitcinenubacter saccharivorans**↓, **Ruminococcum bromii**↓, **Blautia faecis**↓, **Butyricoccus pullicaeorum**↓, **Intestimomas butyricproducens**↑ |
| Zuo et al. (2021b) | **Pepper Mild Mottle Virus (PMMoV)**↑, **Eukaryotic viruses particularly environment-derived eukaryotic viruses with unknown host↑**, **Streptococcus phage↑**, **Escherichia phage↑**, **Homavirus↑**, **Lactococcus phage↑**, **Rallostia phage↑**, **Solumvirus↑**, **Microcystis phage↑** |
| Khan et al. (2021) | **Firmicutes↑**, **Bacteroidetes↑**, **Proteobacteria↑**, **Actinobacteria↑** |
| Hegazy et al. (2021) | **Severe cases**: **Bacteroides plebeius**↑, **Faecalibacterium prausnitzii↑**, **Roseburia faecis↑**, **Bifidobacterium spp↑**, **Bacteroides caccae↑**, **Bacteroides ovatus↑**, **Bacteroides fragilis↑**, **Ruminococcus gravis↑**, **Clostridium boedteae↑**, **Clostridium citroniae↑**, **Clostridium hathewayi↑**, **Parabacteroides distasonis↑** |
| Wang et al. (2021b) | **Intestinal microbiota disturbance and SARS-CoV-2 viral loads**: Prevotella copri and Eubacterium dolchum were positively correlated and Streptococcus anginosus, Dialater spp., Alstipes spp., Ruminococcus spp., Clostridium citroniae, Bifidobacterium spp., Haemophilus spp., and Haemophilus parainfluenzae were negatively correlated with the viral load of SARS-CoV-2. |

COVID-19 patients and a negative correlation with *Clostridium butyricum*. In addition to the innate immunity, gut microbiota improves the function of CD8+ T-cell effectors (Trompette et al., 2018). There is also evidence that few bacterial species such as *Bacteroides ovatus, Lachnospiraceae bacterium 5_1, 63FAA*, and *Eubacterium ventrioium* have an anti-inflammatory property in CD4+ and CD8 T cells (Cao et al., 2021). Natural killer (NK) cells and B cells are also affected by gut microbiota; *Coprobacillus spp., Clostridium ramosum*, and *Clostridium symbiosum* are negatively associated with NK cell activity and Bacteroides *uniformis*, *Faecalibacterium prausnitzii*, and *Subdoligranulum* are positively correlated with B cells (Cao et al., 2021).

We found that the dysbiosis of gut microbiota may be a determinant factor in the clinical severity of COVID-19. Increase of the dominant *Enterococcus* and reduction of *Ruminococcaceae* and *Lachnospiraceae* are reported in severe cases of COVID-19 who were admitted to the medical intensive unit (MICU) (Gaibani et al., 2021).

Diversity of gut microbiota reduces in patients with COVID-19, which is associated with pro-inflammatory reaction and increased risk of opportunistic infections. GI symptoms of COVID-19 are reported to be strongly affected by gut microbial composition (Din et al., 2021; Katz-Agranov and Zandman-Goddard, 2021). The expression of the ACE-2 receptor on the surface of small intestine epithelial cells has been significantly associated with the extent of GI symptoms and fecal viral shedding during the course of disease (D’Amico et al., 2020; Patel et al., 2020; Wu et al., 2020; Katz-Agranov and Zandman-Goddard, 2021; Suárez-Fariñas et al., 2021). An increased expression of ACE-2 receptor in COVID-19 may occur due to a dominance of *Coprobacillus* in gut microbiota (Geva-Zatorsky et al., 2017; Enaud et al., 2020; Zuo et al., 2020a; Massip Copiz, 2021; Rajput et al., 2021; Walton et al., 2021). It is also noteworthy to imply that the expression of ACE-2 on luminal cells may be a determinant factor in microbial composition as the ACE-2 receptor plays some role in amino-acid absorption (Harmer et al., 2002; Dang and Marsland, 2019).

*Eggerthella* is another genus of bacteria which significantly increases in patients with COVID-19 (d’Ettorre et al., 2020; Cao et al., 2021). *Eggerthella* may induce colitis via abnormal activation of Th17 in patients with inflammatory diseases. It can interfere with gut integrity and make the patient more susceptible to pathogen invasion including SARS-CoV-2 (Alexander et al., 2019; Katz-Agranov and Zandman-Goddard, 2021).

There is a dominance of genus *Clostridium* in patients with COVID-19 (Gu et al., 2020b; Zuo et al., 2020a; Cao et al., 2021; Yamamoto et al., 2021). The increase in *Clostridium ramosum* and *Clostridium hathewayi* is associated with the disease severity which may be a risk factor of acute portal vein thrombosis (Zuo et al., 2020a; Rokkam et al., 2021). *Clostridium difficile* may complicate COVID-19 and worsen the GI symptoms (Ferreira et al., 2020; Oba et al., 2020; Sandhu et al., 2020; Khanna and Kraft, 2021). Two butyrate-producing members of this genus, *Clostridium butyricum* and *Clostridium leptum*, are decreased in patients with COVID-19 (Tang et al., 2020).
Streptococcus is another important bacterial genus which increases in COVID-19 (d’Ettorre et al., 2020; Donati Zeppa et al., 2020; Gu et al., 2020b; Zuo et al., 2021a). The abundance of Streptococcus is also an indicator of the extent of opportunistic bacterial invasion (Weiser et al., 2018; Tao et al., 2020). Streptococcus abundance is associated with more expressions of IL-18, TNF-α, and IFN-γ and other inflammatory cytokines worsening clinical outcomes (Tao et al., 2020; van der Lelie and Taghavi, 2020; Chhibber-Goel et al., 2021). An altered gut integrity affected by dysbiosis and inflammatory cytokines seems to be the main cause of increase in Streptococcus abundance in COVID-19 (Donati Zeppa et al., 2020). Streptococcus also affects the lung microbiome with proinflammatory activity (Kyo et al., 2019; Yamamoto et al., 2021).

Genus Rothia dominance increases in patients with COVID-19 (Gu et al., 2020b; Lv et al., 2021a). This genus seems to be associated with inflammatory lung injuries (Han et al., 2020; Chattopadhyay and Shankar, 2021).

The genus Collinsella is an opportunistic pathogenic genus which is widely found in the gut of patients with COVID-19 especially in severe cases and higher infectivity status (Chhibber-Goel et al., 2021; Liu et al., 2021; Massip Copiz, 2021; Rajput et al., 2021; Zuo et al., 2021a). Collinsella aerofaciens abundance altered with the gut mucosal integrity and production of inflammatory mediators such as IL-17, CXC1L, and CXCL5 from the luminal cells (Kalinkovich and Livshits, 2019).

The alteration of genus Parabacteroides in COVID-19 is an area of controversy (Tang et al., 2020; Tao et al., 2020; Chhibber-Goel et al., 2021; Zuo et al., 2021a; Yeoh et al., 2021). It has been suggested that higher levels of Parabacteroides in microbiota are associated with better gut mucosal integrity (Venegas et al., 2019; Tang et al., 2020; Chhibber-Goel et al., 2021).

Ruminococcus species such as Ruminococcus gravis and Ruminococcus torques increase (Cao et al., 2021; Yeoh et al., 2021), and species including Ruminococcus bromii, Ruminococcus obeum, and Ruminococcus sp. 5139BFAA are reduced in patients with COVID-19 (Zuo et al., 2020a; Cao et al., 2021; Lv et al., 2021). Ruminococcus gravis and Ruminococcus torques are known as proinflammatory bacteria which previously have been shown to be associated with proinflammatory status and higher production of inflammatory mediators (Matsuoka and Kanai, 2013; Hall et al., 2017; Henke et al., 2019; Yeoh et al., 2021). Reduction of Ruminococcus obeum seems to be secondary to the wide use/misuse of antibiotics in the management of COVID-19 patients (Cyprian et al., 2021). Among Alistipes genera, Alistipes_sp_AP11, Alistipes indistinctus, and Alistipes shahii are reduced and Alistipes onderdonkii increased in COVID-19 (Zuo et al., 2020a; Cao et al., 2021). Alistipes onderdonkii is one of the most important sources of short-chain fatty acid (SCFA) production in the gut that helps to the gut homeostasis (Venegas et al., 2019; Tang et al., 2020). Alistipes is also important in preservation of the gut immunity via being involved in tryptophan synthesis pathways (Gao et al., 2018).

Bacteroides alteration is reported in COVID-19, especially in critically ill patients (Tang et al., 2020; Cao et al., 2021; Chattopadhyay and Shankar, 2021; Yeoh et al., 2021; Zuo et al., 2021a). Bacteroides are the most critical commensal bacterial genera in gut whose alterations are associated with several conditions affecting human health and disease (Ley et al., 2006; Turnbaugh et al., 2006; Larsen et al., 2010; Claesson et al., 2012; Yu et al., 2015; Boursier et al., 2016; Salazar et al., 2017; Belizário et al., 2018; O’Toole and Jeffery, 2018; Yildiz et al., 2018; Antosca et al., 2019; Rahayu et al., 2019; Crovesy et al., 2020; Juárez-Fernández et al., 2021). Bacteroides also have immunomodulatory effects, which is mainly mediated by alterations in production of polysaccharide A, IL-6, IL-7, IL-10, dendritic cells, and CD4+ and CD8+ T cells (Abt et al., 2012; Zhang et al., 2018; Jia et al., 2018; Ramakrishna et al., 2019; Alvarez et al., 2020; Gautier et al., 2021). Bacteroides are also associated with reduction of the expression of the ACE-2 receptor (Chattopadhyay and Shankar, 2021). Use of antibiotics seems to result in increase of Bacteroides caccae in a COVID-19 patient. In antibiotic-naive COVID-19 patients, Bacteroides nordii are more common (Chattopadhyay and Shankar, 2021). On the other hand, species such as Bacteroides massiliensis, Bacteroides dorei, Bacteroides thetaiotaomicron, and Bacteroides ovatus decrease in SARS-CoV-2 infection (Zuo et al., 2020a; Cao et al., 2021). Bacteroides dorei itself is a controversial bacterium with both evidence of increase and decrease in COVID-19 patients. This species is associated with IL-6 and IL-8 and downregulation of the ACE-2 receptor (Yoshida et al., 2018; Yeoh et al., 2021).

Bifidobacterium, a major bacterial genus in the gut, reduces by SARS-CoV-2 (Gu et al., 2020b). In patients who received fecal microbial transplant (FMT), a re-expansion of Bifidobacterium in their gut was demonstrated (Liu et al., 2021). Bifidobacterium spp. are well known for their immunomodulatory effects especially on Th17 and in the amelioration of inflammatory processes (de Vrese et al., 2005; Wang et al., 2011; Groeger et al., 2013; Jungersen et al., 2014; King et al., 2014; Han et al., 2016; Schiavi et al., 2016; Bozkurt et al., 2019; Bozkurt and Kara, 2020; Tian et al., 2020; Arenas-Padilla et al., 2021; Chen and Vitetta, 2021; Hong et al., 2021; Milner et al., 2021). Bifidobacterium may be considered as a supplemental therapeutic agent for controlling cytokine storm and inflammation in patients with COVID-19 (Bozkurt and Quigley, 2020; Bozkurt and Quigley, 2020a; Schett et al., 2020; Bhushan et al., 2021; Gautier et al., 2021; Mohseni et al., 2021).

Faecalibacterium decreases in COVID-19 and has been related to the severity of disease (Zuo et al., 2020; Gu et al., 2020; Tang et al., 2020; Yamamoto et al., 2021; Lv et al., 2021). Faecalibacterium is a butyrate-producing genus which positively impacts on intestinal mucosal integrity and is also known to have anti-inflammatory effects (Alameddine et al., 2019; Zuo et al., 2020a; Chhibber-Goel et al., 2021). Fecal transplantation significantly increases the abundance of Faecalibacterium in discharged patients with COVID-19 and has been shown to improve the inflammation states (Sokol et al., 2008; van den Munckhof et al., 2018; Venegas et al., 2019; Liu et al., 2021).

Lachnospiraceae, which is known as SCFA-producing bacteria, decreases in patients with COVID-19 (d’Ettorre et al., 2020; Gu et al., 2020b; Zuo et al., 2020a; Cao et al., 2021; Gaibani et al., 2021; Gautier et al., 2021; Zuo et al., 2021a). It may be
attributed to common use of azithromycin and other antibiotics in the management of COVID-19 (Segal et al., 2020).

Genus *Roseburia* is another commensal gut microbiota which decreases in patients with COVID-19 and other viral diseases such as influenza (Wang et al., 2017; Gu et al., 2020b; Cao et al., 2021; Lv et al., 2021a). SCFAs produced by *Roseburia* maintain mucosal integrity in healthy adults via modulation of inflammatory mediators especially IL-10 (Koh et al., 2016; Zheng et al., 2017; Haak et al., 2018; Gautier et al., 2021). It has been shown previously that butyrate may preserve lung integrity from cytokine-induced injuries in influenza (Chakraborty et al., 2017; Dang and Marsland, 2019). If we assume that it is true in COVID-19, lower levels of *Roseburia* result in lower levels of butyrate and consequently more extensive lung injuries due to inflammatory processes.

*Eubacterium* is a genus with immunomodulatory effects which significantly decrease in gut microbiota of patients with COVID-19 (d’Ettorre et al., 2020; Zuo et al., 2020a; Gu et al., 2020b; Cao et al., 2021; Chattopadhyay and Shankar, 2021; Gautier et al., 2021; Lv et al., 2021; Yeoh et al., 2021). Wide use of antibiotics is considered to be associated with reduction of this genus (Zuo et al., 2020a). This genus similar to *Roseburia* spp. produces butyrate and modulates inflammation in inflammation-mediated injuries (Koh et al., 2016; Zheng et al., 2017; Haak et al., 2018; Gautier et al., 2021).

*Fusicatenibacter* is another bacterial genus that reduced during the course of COVID-19 (Gu et al., 2020; Chattopadhyay and Shankar, 2021; Lv et al., 2021a). *Fusicatenibacter* alteration is a very sensitive biomarker during COVID-19. It is proposed to be a diagnostic tool for COVID-19 (Gu et al., 2020b; Segal et al., 2020; Cyprian et al., 2021; Howell et al., 2021). This genus is also negatively correlated with CRP and procalcitonin levels in patients with COVID-19 (Gu et al., 2020b).

Other members of the gut microbiota are viruses and fungi. Although pathogenic gut viruses are known for more than a century, the term “gut virome” is recently introduced (Reyes et al., 2012). Most of the gut virome consists of bacteriophages that can explain the fact that the virome structure is related to gut bacterial composition in both healthy and COVID-19 people (Minot et al., 2011; Cao et al., 2021). There is a bidirectional relationship between gut virome and infectious diseases; bacteriophages have a significant role in protecting against bacterial infections (Wilks and Golovkina, 2012). Gut virome composition might be affected during COVID-19 (Cao et al., 2021). There are limited data on the alterations of commensal viral and fungal populations in the gut during COVID-19 infection.

Lv et al. showed a strong correlation between altered fungal gut microbiome and inflammatory blood biomarkers (Lv et al., 2021b). Further studies focusing on viral and fungal alterations during the COVID-19 are desired.

The gut microbiota alteration in COVID-19 patients should be considered as a dynamic process (d’Ettorre et al., 2020; Liu et al., 2021; Hussain et al., 2021; Zuo et al., 2020a). To the date of revising this manuscript (January 2022), several registered clinical trials are in progress and the results are not provided yet; however, growing evidence supports the effectiveness of microbiota modulatory actions on fastening the recovery of patients with COVID-19 (Chen and Vitetta, 2021; Hussain et al., 2021; Wang et al., 2021a).

**Limitations and Suggestions**

A few studies have documented the comorbidities of subjects. However, almost all the studies have missed the impact of comorbidities on gut microbiota alterations in COVID-19 patients compared with the healthy control. It has been shown that gut microbiota may change in patients with hypertension, cardiovascular diseases, diabetes mellitus, hyperlipidemia, and thrombotic events (Huynh, 2020; Avery et al., 2021; Kyriakidou et al., 2021; Mineshita et al., 2021). We strongly propose to investigate the effects of underlying comorbidities in gut microbial composition in patients with COVID-19.

Due to the variations in data analysis techniques such as 16S rRNA sequencing, qPCR, and metagenome sequencing, there was a challenge to compare the bacterial taxa across studies. Since there was a fair diversity in geographical distribution of the current studies (most of them are from China), we cannot ignore the effect of diet and genetic predisposing factors like HLA in gut microbiome compositions. Future studies in different countries are required in this regard.

It is important to mention that different levels of p-value significance were reported in reviewed articles; however, in this study we used only statistically significant findings from the included studies.

Further studies with a larger study population, including the range of patients from mild to severe symptoms, involving the patients who are managed out patiently, focusing on the effectiveness of gut microbiota-targeted therapies for prevention and improvement of COVID-19 patients’ symptoms are desired to light up this topic.

**CONCLUSION**

Our study showed a significant alteration of gut microbiome composition in patients with COVID-19 compared to healthy individuals. This great extent of impact has proposed the gut microbiota as a potential diagnostic, prognostic, and potentially therapeutic strategy for COVID-19.

**AUTHOR CONTRIBUTIONS**

MN and PJ designed the study. MN, YF, AT, PJ, MA, and FV performed the search and data extraction and wrote the first draft of the manuscript. LS, AHSB, and MM reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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