Aberrant Human Gut Microbiome Composition in COVID-19 Disease: A Potential Target for Novel Adjuvant Therapy

CINDY LU

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The COVID-19 pandemic has created a global emergency that calls for a better understanding of our immune defenses against SARS-CoV-2. It has been shown that some gut bacteria have immunomodulatory properties, and emerging evidence has indicated the possible association of the irregular gut microbiome composition in COVID-19. However, the heterogeneity amongst the original research studies' results requires thorough statistical analysis to reach a unified conclusion. This study aims to examine the relationship between human gut microbiome composition and COVID-19. Three databases including PubMed, Web of Science, and Embase were searched to find articles published prior to February 2022 that reported measures of gut bacterial composition in COVID-19 patients. The abstracts of these articles were screened to determine if they fulfilled the selection criteria and eventually, 11 publications containing appropriate information were selected and analyzed. Microbiome composition data were evaluated using alpha diversity, beta diversity, and relative abundance indexes to determine if the composition of gut microbiome in COVID-19 patients is different from the healthy control group. The results of this study suggest that COVID-19 patients are associated with abnormal microbiome composition, as reflected by a statistically significant decrease in microbial diversity as compared to healthy individuals. In addition, COVID-19 patients exhibited notably decreased anti-inflammatory bacteria, but increased opportunistic bacteria. These findings indicate that gut microbiome can be used as a biomarker in monitoring COVID-19 disease progress, and restoring the diversity and number of antiinflammatory bacteria may serve as a promising novel adjuvant therapy.

1 Introduction

COVID-19 caused by SARS-CoV-2 has rapidly spread worldwide, resulting in over 400 million infections and 5 million deaths globally since December 2019 [13]. It is a respiratory disease with a broad range of clinical manifestations, and the symptoms can range from mild with fever and cough to severe pneumonia and multiple organ failures. Infection by SARSCoV-2 induces an immune response to eradicate the virus, but plenty of evidence have suggested that an aberrant immune response is responsible for severe illness and damages in the lung and other organs. It is also common that after the patients have recovered from the acute phase of the disease, long term implications on the body remain [14]. The severity of this disease has elicited the development of multiple COVID-19 therapies, most of which are focused on virus clearance, such as neutralizing monoclonal antibodies and small molecule drugs targeting the viral protease or RNA polymerase. However, due to the long-lasting effects of SARS-CoV-2 infection on the human body even after viral clearance, it is necessary to develop novel therapy that allows patients to fully recover from the serious damages caused by COVID-19. The gut microbiome is the collection of a tremendous number of gut microorganisms living in symbiosis with human that contribute to human health. The gut microbiome is involved in the host nutrient metabolism, drug metabolism, protection from pathogens, and maintenance of structural integrity of the intestinal mucosal barrier. Studies in recent years have shown that the gut microbiome also plays an essential role in the regulation of the host immune system. It is very important to maintain a healthy gut microbiome, and the imbalance of microbiome is implicated in metabolic diseases,

autoimmune and inflammatory diseases, neurodegenerative disorders, and cardiovascular diseases [10]. The goal of this study was to systematically review the emerging evidence on the association of gut microbiome alterations and COVID-19 and the potential of using gut microbiome composition as a biomarker for monitoring the disease progression and treatment effectiveness, and to development of potential new adjuvant therapy for COVID-19.

2 Methodology

A systematic review on the original clinical articles for evaluating the human gut microbiome in COVID-19 was conducted. The "preferred reporting items for system review and metaanalysis" (PRISMA) reporting guidelines [9] were followed.

2.1 Database search strategy

PubMed, Embase, and Web of Science were searched to identify articles with original data that were published before February 1, 2022. Search terms or keywords include: "COVID-19," "COVID 19," SARS-CoV-2 Infection," "Gastrointestinal Microbiome," and "Gut Microbiome."

2.2 Selection Criteria

Publications were screened and selected using the principles of PICOS, a framework frequently used in systematic reviews to ensure comprehensive and bias-free searches OR to formulate eligibility criteria in systematic reviews. The population (P) were patients with confirmed SARS-CoV-2 infection. The intervention (I) was gene sequencing for the intestinal microbiome. The comparison (C) was against intestinal flora in healthy conditions. The outcomes (O) were measures of gut microbiota composition. The study (S) type was observational study.

2.3 Data Extraction and Analysis

Publications details, including number of patients and methodological information, were extracted. The community-level measures of gut microbiota composition (using alpha and beta diversity indexes) and taxonomic findings at the phylum and species levels (using relative abundance indexes) were then determined. Alpha diversity provides an overview of microbial communities in individual samples and can be compared across groups to assess the richness (number of species) and uniformity (representation of each species) of the samples. Beta diversity is a measure of diversity among individuals (between samples). It evaluates the similarity between the community and control samples analyzed [1, 16]. For the relative abundance of microbial groups, we conducted qualitative synthesis.

3 Results

The initial search in the database PubMed, Embase, and Web of Science identified 1235 papers. After exclusion of the duplications, irrelevant publications and publication containing studies lacking controls, 11 original studies were kept according to the inclusion criteria. The systematic literature review flowchart is shown in Figure 1 and the basic information of each study is shown in Table 1. A total of 436 patients with COVID-19 infection and 336 healthy people were included in the analysis.

3.1 COVID-19 patients have reduced diversity in gut microbiome

Nine studies reported the Shannon index to demonstrate the diversity richness of the gut microbiome. In these studies, stool samples from the COVID-19 patients and healthy participants were collected and the microbiome components were determined by gene sequencing. Shannon index was calculated to show the diversity. Six of the nine studies provided data that were included in the meta-analysis (230 patients and 182 controls) [3, 5, 15, 17, 18, 19]. Although there is great heterogeneity between the studies (I2=91.2%), the pooled estimate demonstrated a significant difference between groups with standardized mean difference (SMD) of -1.13 [-1.97 to -0.30] when the confidence interval (CI) is 95%. p value is less than 0.001 (Figure 2) indicating that the difference observed in the COVID-19 patients and healthy individuals is statistically significant. These findings demonstrate that infection with SARSCoV-2 reduced the diversity of intestinal microbiome.

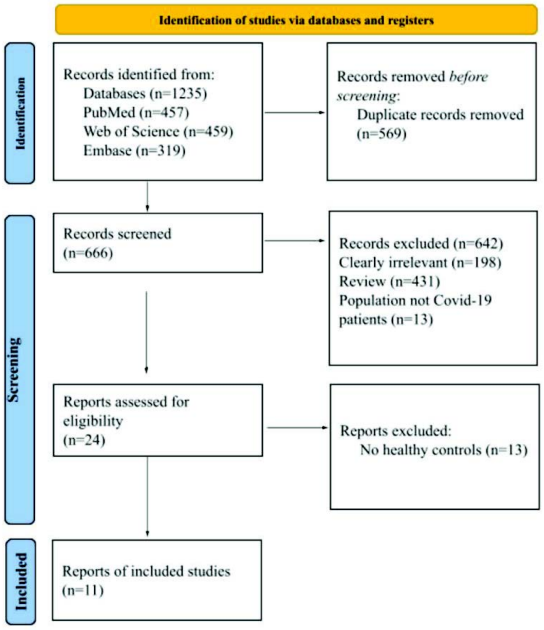

Figure 1: Flowchart of Literature Inclusion.

Table 1: Basic Information of literature included in the study.

No.	Authors	Year	Covid-19 (n=)	Control (n=)
1	Lanjuan Li et al.[12]	2020	30	30
2	Andreas Henschel et al.[2]	2021	86	57
3	Jiabao Cao et al.[3]	2021	13	5
4	Paolo Gaibani et al.[4]	2021	69	69
5	Sabine Hazan et al.[8]	2021	50	20
6	Mahejibin Khan et al.[11]	2021	30	10
7	Sijia Li et al.[12]	2021	47	19
8	Lanjuan Li et al.[15]	2021	24	48
9	Yun Kit Yeoh et al.[18]	2021	87	78
10	Xun Li et al.[19]	2021	13	13
11	Yan-Mei Chen et al.[17]	2022	63	8

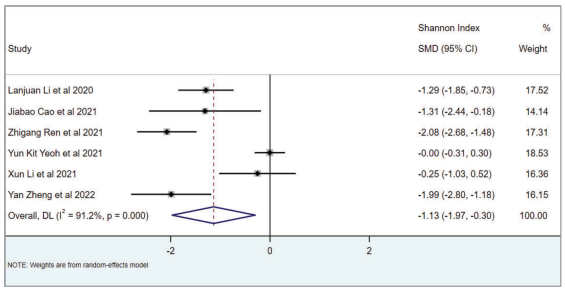

Figure 2: Forest Plots of Alpha Diversity in the gut microbiota of patients with SARS-CoV-2 infection compared with healthy controls (Shannon Index).

3.2 Composition of gut microbiome in COVID-19 patients is significantly different from healthy people

In five of the eleven studies, difference tests were performed based on principal component analysis. The results of β diversity analysis are summarized in Table 2. The five studies showed that the composition of intestinal flora after infection with COVID-19 was significantly different from that of healthy people.

Table 2: Beta Diversity in the Gut Microbiota of Patients With SARS-CoV-2 infection Compared with Healthy Controls.

Study	Year	Metric	Analysis	Finding
Lanjuan Li et.al [5]	2020	China	ANOSIM	significantly different in COVID-19 patients
Jiabao Cao et.al [3]	2021	UAE	PERMANOVA	significantly different in COVID-19 patients
Paolo Gaibani et.al [4]	2021	China	permutation test with pseudo-F ratio	significantly different in COVID-19 patients
Sijia Li et.al [12]	2021	Italy	ANOSIM	significantly different in COVID-19 patients
Yan-Mei Chen et.al [17]	2022	USA	PERMANOVA	significantly different in COVID-19 patients

3.3 COVID-19 patients exhibited significant changes in relative abundance of certain gut bacteria: anti-inflammatory bacteria were reduced, opportunistic pathogens were increased

At the genera and species level, the relative abundance of pathogenic bacteria and opportunistic pathogens increased in COVID-19 infected patients, such as Ruminococcus gnavus, Bacteroides ovatus, Streptococcus, Causing intestinal inflammation. The relative abundance of some beneficial bacteria decreased, including Bifidobacterium, Faecalibacterium prausnitzii and Clostridium nexile. Result was summarized in Table 3.

Table 3: Relative abundance in COVID-19 patients at the species level.

Species	Increase	Decrease
Lanjuan Li et.al [5]	Streptococcus, Faecalibacterium	Bifidobacterium
Andreas Henschel et.al [2]	Streptococcus	Bifidobacterium
Jiabao Cao et.al [3]	Ruminococcus gnavus	Bacteroides massiliensis
Paolo Gaibani et.al [4]	Enterococcus faecium, Staphylococcus	-
Sabine Hazan et.al [8]	-	Bifidobacterium
Mahejibin Khan et.al [11]	Parabacteroides, Ruminococcus gnavus	Bifidobacterium
Sijia Li et.al [12]	Bacteroides stercoris, Bacteroides vulgatus	Clostridium nexile
Yun Kit Yeoh et.al [18]	Ruminococcus gnavus, Ruminococcus torques, Eubacterium rectale	Bifidobacterium adolescentis
Yan-Mei Chen et.al [17]	Bacteroides ovatus, Acinetobacter bereziniae	Bifidobacterium pseudocatenulatum, Faecalibacterium prausnitzii

4 Discussion and Conclusion

This study demonstrated the association of aberrant gut microbiome and COVID- 19 disease, as reflected in significantly decreased microbial diversity and altered microbial composition. At the genera and species level, the relative abundance of immunomodulatory bacteria decreased, including Bifidobacterium, Faecalibacterium prausnitzii and Clostridium nexile, while there was an increase in the abundance of pathogenic bacteria and opportunistic pathogens. This study provides important guiding information for the treatment of COVID-19. The gut microbiome will serve as a biomarker to monitor the disease progression and treatment effectiveness. Full recovery of the healthy microbiome may be used as one of the indications for the recovery of the patients. Secondly, restoring gut microbiome can be used as an adjuvant therapy to treat COVID-19 patients. COVID-19 can involve sequelae and a broad range of medical complications that last months after the initial recovery. Coincidently, the perturbation of gut microbiome in COVID-19 patients can also last months after recovery. As gut microbiome plays an important role in many host functions including metabolism, strengthening gut integrity, and regulating host immunity, restoring the

gut microbiome by supplementing with beneficial microorganisms may serve as a promising novel adjuvant therapy during the disease phase as well as to treat the long-lasting complications of COVID-19.

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